The impact of urinary tract infections in renal transplant recipients

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Urinary tract infections (UTIs), including cystitis and pyelonephritis, are the most common infections after kidney transplantation. On examining the role of surveillance and treatment of asymptomatic bacteriuria posttransplant, Fiorante and colleagues found that up to 50% of recipients had bacteriuria. Despite routine treatment, recurrent UTIs remained common. Many risk factors contribute to the high incidence of UTIs, which can undermine graft function and survival. Given that many UTIs are asymptomatic, screening protocols may be beneficial.


Urinary tract infection (UTI)—including asymptomatic bacteriuria, cystitis, and pyelonephritis—is the most common form of bacterial infection following renal transplantation.1 For example, in the recent ELITE-Symphony trial,2 approximately 25% of patients had symptomatic UTIs during the first year after transplantation regardless of the immunosuppression protocol used. However, the fact that posttransplant UTIs are often asymptomatic suggests that the magnitude and implications of this problem are larger than is generally appreciated. The study by Fiorante et al.3 in this issue of Kidney International provides direct evidence of this, the authors having shown that bacteriuria and/or cystitis affects at least 50% of transplant recipients and is often recurrent. It is difficult to assess the incidence of pyelonephritis after kidney transplantation because these infections may either be asymptomatic or have an atypical clinical presentation, as discussed below. Therefore the diagnosis of allograft pyelonephritis on clinical grounds may be of questionable accuracy.

UTIs after kidney transplantation have important implications. They may be associated with bacteremia and may require hospitalization. The recurrent nature of the problem necessitates the use of multiple courses of antibiotic therapy, which are not only costly but can result in bacterial resistance and contribute to erratic levels of immunosuppression. Repeated infections may also lead to graft inflammation and fibrosis4—an observation supported by the current study of Fiorante et al. A previous large retrospective review found that UTIs occurring more than 6 months posttransplant were associated with an increased risk of graft loss and even death.5 Likewise, allograft pyelonephritis has been associated, at least in some studies, with reduced allograft function1,6 and may lead to graft loss.7 However, it is possible that pyelonephritis is more common than we clinically suspect; thus the impact of allograft infection on graft function and survival may be underestimated. This postulate is supported by a recent report of 40 cases of allograft pyelonephritis diagnosed by either protocol or clinical biopsy (abstract presented at the 2009 annual meeting of the American Society of Nephrology). In most of these cases the disease was not suspected clinically. Interestingly, many of the cases of pyelonephritis were associated with preceding episodes of ‘uncomplicated’ UTI that had been treated. Despite the high incidence and detrimental impact of posttransplant UTIs, specific guidelines regarding screening and management are lacking. Current guidelines simply recommend that kidney transplant recipients receive posttransplant UTI prophylaxis with trimethoprim–sulfamethoxazole and that patients with allograft pyelonephritis receive intravenous antibiotics in the hospital.8

Many factors are thought to contribute to the high incidence of posttransplant UTI (Figure 1). Some exist prior to transplant, including female sex, diabetes mellitus, and underlying urinary tract abnormalities. In addition, peritransplant factors are important and are often related to instrumentation of the urinary tract, including ureteral stenting and prolonged urinary catheterization. Of interest are some studies showing that recipients of kidneys from deceased donors may also be at higher risk of UTIs than recipients of living-donor grafts. We postulate that this association may be related to the higher incidence of delayed graft function after transplantation with a deceased-donor organ and/or to bladder dysfunction after a prolonged time on dialysis. The importance of the latter factor, in our opinion, cannot be overestimated. It is indeed a challenge to evaluate the functional capacity of the urinary tract in kidney transplant candidates who have been on dialysis for prolonged periods of time because these patients produce very little urine. They frequently have bladders with very small capacities and significant dysfunction. Furthermore, significant bladder outlet obstruction, particularly in males, may not be appreciated until after the transplant, leading to prolonged instrumentation and an increased risk of UTI.

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Additional risk factors contributing to UTI posttransplant include immunosuppression and graft dysfunction or rejection. It is noteworthy that there is no clear association between the risk of UTI and dose or type of maintenance immunosuppression. In addition to these factors, in our clinical practice we have been impressed with the frequent association between repeated episodes of UTI and diarrhea, a common and often troublesome posttransplant complication. This association has not been described in previous studies, but it is useful to recognize because resolution of recurrent UTIs in these patients requires treatment of the diarrhea. Posttransplant UTIs are most frequent during the first year after surgery, suggesting that perioperative factors and perhaps the higher levels of immunosuppression used during the first year after transplantation are major contributors to risk.

In this issue of Kidney International, Fiorante and colleagues report a single-center retrospective study describing the results of a protocol involving surveillance for asymptomatic bacteriuria (AB) in kidney transplant recipients. It should be noted that this center’s protocol includes routine antimicrobial treatment of AB—a feature that limits the authors’ ability to assess the implications of AB when left untreated. Still, this study provides important and useful information about UTI after transplantation. First, the authors found that 51% of patients developed at least one episode of AB during their first 3 posttransplant years. Notably, this is a significantly higher incidence than that described for symptomatic UTI, illustrating once again that UTIs are a problem of larger magnitude than is commonly appreciated. It is striking to note that although the authors searched systematically for bacteriuria and treated most episodes of AB, symptomatic cystitis and clinically diagnosed pyelonephritis still occurred in 12% and 13% of patients, respectively. The authors identified ‘double renal transplants’ (that is, transplantation of two kidneys from the same donor en bloc) as a risk factor for UTI. This association is perhaps expected, given the more complex urinary tract anatomy in these instances. The association described in this manuscript between the pretransplant diagnosis of ‘glomerulonephritis’ and UTI is less intuitive and deserves reexamination in future studies.

Unfortunately, the study by Fiorante et al., does not answer the question of whether surveillance and treatment of AB after kidney transplantation are clinically useful exercises because most of their patients with AB had received antimicrobial treatment. Indeed, the utility of UTI surveillance programs is not a foregone conclusion. Thus, although these protocols are useful in pregnancy and in patients undergoing urologic procedures, they do not appear to be useful in patients with diabetes. In our opinion, the lack of association between treated AB and graft function, proteinuria, or graft survival in the present study should not be interpreted as indicating that AB is clinically irrelevant. It is interesting that, despite aggressive therapy, repeated episodes of AB were still associated with an increased risk of pyelonephritis, suggesting that either the antimicrobial therapy was ineffective or additional risk factors—perhaps related to anatomy or instrumentation—played a role. In that respect, it appears that 30% of the patients with AB did not receive antimicrobial treatment. However, the authors did not provide information about the outcome of this subgroup of patients. The retrospective nature of the Fiorante study indeed makes causality very difficult to determine. It should be noted that the study cohort included few patients with diabetes (and despite this the incidence of AB was very high!) and no recipients of living-donor kidney transplants.

Notwithstanding the limitations noted above, Fiorante et al. should be applauded for undertaking this study, for providing important new information about UTIs after kidney transplantation, and for pointing out the general lack of knowledge regarding this important topic. Clinical studies in kidney transplant recipients generally focus on major posttransplant events such as acute rejection, immunosuppression, and graft or patient survival. However, the practice of kidney transplantation has changed dramatically in recent years, with a marked reduction in the risk of acute rejection and improvements in antibiotics and immunosuppressive drugs. As the risk of graft injury from processes such as acute rejection declines, the importance of allograft injury from other mechanisms, previously considered less important, increases in relevance. In that respect, infections—particularly those affecting the urinary tract—are well deserving of investigation. Improvements in the prevention and care of these infections will probably also improve patient satisfaction, reduce hospitalizations and costs, and in some patients result in improved graft function and survival. Indeed, these are lofty goals.

**DISCLOSURE**

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**REFERENCES**

2. Ekberg H, Tedesco-Silva H, Demirbas A et al. Reduced exposure to calcineurin inhibitors in
Atypical hemolytic uremic syndrome: telling the difference between H and Y

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Mutations in the complement factor H (CFH) gene are frequently associated with atypical hemolytic uremic syndrome (aHUS). Hakobyan et al. have developed novel reagents that can rapidly determine the contribution of each CFH allele to the total plasma CFH pool, showing that low-expression CFH alleles are important risk factors for the development of aHUS. These reagents represent a significant contribution to the techniques used to determine susceptibility factors among individuals with aHUS.


The hemolytic uremic syndrome (HUS, MIM 235,400) is a condition characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure due to glomerular thrombotic microangiopathy. The majority of HUS episodes are triggered by Escherichia coli 0157:H7 infection. However, a minority of cases are not associated with infection; this form, termed atypical HUS (aHUS), has the poorest long-term prognosis. During the last decade there has been dramatic progress in understanding the pathogenesis of aHUS, particularly through the study of familial forms. Approximately half of all aHUS cases have been associated with mutations and/or polymorphisms in genes encoding proteins of the complement system. Mutations in the regulatory proteins of this system resulted in ‘loss of function,’ whereas mutations in genes encoding complement activation proteins resulted in ‘gain of function.’ Mutations in thrombomodulin, an endothelial glycoprotein, have recently been associated with aHUS. These mutations were associated with impaired complement regulation in vitro. Together with other lines of evidence, aHUS is now viewed as a disorder in which there is defective complement regulation (Figure 1).

In many individuals, both genetic susceptibility factors and an environmental insult are required for the syndrome to develop. For example, many environmental factors—such as infection, pregnancy, and drugs—have been reported to trigger episodes of aHUS. Family studies have clearly shown that multiple genetic risk factors are generally required for the condition to become manifest. For example, in one pedigree in which there were three independently segregating aHUS-associated risk factors, the syndrome developed only among individuals possessing all three risk factors.

The investigation of individuals with aHUS for genetic susceptibility factors has become increasingly complex because both the number and nature of reported genetic defects has expanded. The diagnostic workup of affected individuals is summarized in Figure 2. Exon sequencing to screen for mutations in complement regulatory (CFH, CFI, and MCP (membrane cofactor protein, also known as CD46)) and activation (C3, CFB) genes and the thrombomodulin gene (THRB) is relatively straightforward. However, significant complexity arises within the CFH gene family. Complement factor H (CFH) is the major regulator of the complement alternative pathway, and mutations in the CFH gene are among the most frequent alterations detected in the majority of aHUS cohorts. The CFH gene is located in the ‘regulators of complement activation’ (RCA) gene cluster on chromosome 1q32.4 The gene encodes the CFH protein, an abundant plasma protein comprising 20 globular domains termed short consensus repeat (SCR) domains. In addition, through alternative splicing, the CFH gene also encodes a smaller protein consisting of only seven SCR domains, termed factor H–like 1 (FHL-1). With the exception of the C-terminal four amino acids, the FHL-1 protein sequence is identical to the first seven SCR domains of CFH. In close proximity...
to the CFH locus are five genes encoding proteins that are structurally related to CFH. These five proteins are termed CFH-related proteins. Their respective genes are arranged in the genomic sequence CFHR3, CFHR1, CFHR2, CFHR4, and CFHR5. The CFH–CFHR1–5 gene region contains multiple genomic duplications that render this area susceptible to genomic rearrangements through mechanisms such as gene conversion or nonhomologous recombination. Some of these rearrangements have been associated with aHUS. Examples include a rearrangement that results in the formation of a CFH–CFHR1 hybrid gene. Furthermore, a common polymorphic rearrangement that results in the deletion of CFHR1 and CFHR3 genes is associated with anti-CFH autoantibodies and aHUS. Identification of these rearrangements requires the use of techniques (such as multiplex ligation-dependent probe amplification analysis) that assess copy-number variation across the CFH–CFHR1–5 gene region.

In addition to genetic analysis, important investigations in aHUS patients include assays to measure plasma complement components (e.g., CFH), measurement of CD46 expression on peripheral blood mononuclear cells, and techniques to detect anti-CFH autoantibodies. Again, the situation for CFH is not straightforward. The normal range for plasma CFH is quite wide and influenced by both genetic and environmental (e.g., smoking) factors. Consequently, heterozygous CFH deficiency states may not be readily detectable by measurement of plasma CFH levels. The difficulty is how to distinguish the contribution of each CFH allele to the plasma CFH pool.

In this issue, Hakobyan et al. report having addressed this problem by developing a novel method to rapidly measure allele-specific CFH protein products (Figure 3). They used the common nonsynonymous CFH polymorphism termed Y402H (rs1061170), located within the SCR7 domain of both CFH and FHL-1, to generate monoclonal antibodies specific for either the Y402 or H402 protein alleles. These reagents allowed the authors to determine, among individuals who are heterozygous for Y402H, the contribution of each CFH allele to the total plasma CFH and FHL-1 protein pool. With these new tools, they assessed plasma levels of the Y402 and H402 protein alleles among individuals with aHUS in their Spanish cohort. Among 48 cases who were heterozygous for Y402H, 3 unrelated individuals with low expression of the H402 allele were identified. In 2 of these (H29 and H90), total plasma CFH levels were in the lower part of the normal range (124.4–402 mg/liter) when a non-allele-specific CFH ELISA was used. In each family, the inheritance of low- or null-expression alleles was an
Figure 3 | Complement factor H and the Y402H polymorphism. Complement factor H (CFH) is a plasma protein comprising 20 globular protein domains termed short consensus repeat domains (SCRs). Distinct SCRs mediate the important functions of CFH. Regulation of C3 is mediated by the initial four amino terminal domains (colored red), and surface recognition domains include terminal two carboxyl domains (green). The Y402H polymorphism (T1204C, rs1061170) is located within SCR domain 7. Hakobyan et al.9,10 have generated antibodies that specifically recognize either the Y402 or H402 CFH and FHL-1 variants. Among individuals who are heterozygous for the Y402H polymorphism (and thus have both 402H CFH and 402Y CFH in plasma), the novel antibodies enable investigators to determine the contribution of each of the two CFH alleles to the total plasma CFH pool. This facilitates rapid detection of CFH null alleles.

independent risk factor for aHUS. Several important messages emerged from the analysis of these individuals.

First, using an ELISA assay, these antibodies provide a rapid and simple tool for the identification of CFH null alleles. In addition, these novel reagents may circumvent the need to perform cloning and expression studies to determine whether a particular mutant affects protein expression. Two of the index cases identified by Hakobyan et al.9 were found to have mutations affecting cysteine residues within the CFH protein (C853R in index case H90 and C1218R in index case H169). Both index cases were heterozygous for the Y402H polymorphism. With the allelotype-specific reagents developed by Hakobyan et al.,9 it was straightforward to demonstrate that these cysteine mutations are associated with no expression of the CFH protein. Using western blotting, it was also possible to show that FHL-1 expression from the affected alleles was normal. This would be expected, since these cysteine mutations affected exons encoding for SCR domains that are not present in the FHL-1 protein. In another report, these reagents were used to demonstrate that the CFH Y899D mutation was associated with minimal protein expression.10

Second, these techniques allowed Hakobyan et al.9 to track two abnormal CFH alleles in another aHUS-affected pedigree. The index case (H29), a Y402H heterozygote, had low levels of the plasma H402 protein allelotype. In contrast, plasma levels of the Y402 protein allelotype were normal. However, this individual carried a common aHUS-associated CFH gene mutation (R1210C) on the CFH Y402 allele. The R1210C mutation was present in heterozygosity in five other members of this pedigree, none of whom had developed aHUS. Two of these individuals, one sister of the index case, were Y402H heterozygotes. Hakobyan et al.9 were able to show that these individuals had not inherited the abnormal low-expressing CFH H402 allele present in the H29 index case. Therefore, in this pedigree, aHUS had developed only when both abnormal CFH alleles were present. Only through the use of these novel reagents was it possible to conclude that the sister of the index case is not at high risk of developing aHUS. This illustrates an important clinical application for these antibodies.

Third, interesting insights into the differential regulation of CFH and FHL-1 emerged from the study of the H29 pedigree. The genetic basis of the low-expression CFH H402 allele was not found, even though an extensive search for the causative mutation was performed. However, although the plasma levels of the CFH 402H allelotype were markedly reduced, western blot analysis surprisingly showed that the FHL-1-H402 allelotype was increased five-fold compared with controls. This suggests that the defect has disrupted differential CFH gene splicing. The significance of this is not clear but warrants further study.

In summary, the investigation of patients with aHUS has become increasingly complex, and in many cases no susceptibility factors have been identified. This indicates that our understanding of the condition remains incomplete. The work of Hakobyan et al.9 provides valuable additional tools for the investigation of patients with aHUS. With the novel reagents developed by these investigators, it is now possible to rapidly identify low-expressing or null CFH alleles. These are independent risk factors for aHUS that should be looked for in other cohorts.

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Ionizing radiation exposure: another underrecognized risk factor for poor health outcomes in dialysis patients

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Dialysis patients are at greater risk for cancers, cardiovascular disease, and all-cause mortality than people in the general population. Novel risk factors have been identified that may help explain these risk elevations. We discuss medical radiation exposure as a novel risk factor in dialysis patients and suggest the need for future research on this topic.


Dialysis patients in the United States and worldwide are at elevated risk for cancers, cardiovascular disease (CVD), and all-cause mortality.¹,² However, the prevalence of known risk factors does not fully explain the higher risks seen in the dialysis population.³ This has led to increased interest in the role of novel risk factors for CVD and malignancies in dialysis patients (Figure 1), and some of the resulting data have been translated to the general population.⁴ In this issue of Kidney International, Kinsella et al.⁵ introduce a new risk factor to the list of novel risk factors in dialysis patients. In this study from Ireland, the researchers follow 100 point-prevalent patients for a median of 3.4 years to assess their medical exposure to ionizing radiation, principally from computed tomography (CT) scans, procedures related to vascular access. In individuals whose occupations expose them to ionizing radiation, guidelines limit annual exposure to less than 20 millisieverts (mSv) per year. Among the Irish dialysis patients, 14% had cumulative effective doses (CEDs) of radiation exceeding 20 mSv per year. Patient characteristics associated with high doses of ionizing radiation included having end-stage renal disease (ESRD) due to diabetes mellitus, having baseline ischemic heart disease, and not being on the kidney transplant list. Patients with more inpatient hospital days had higher CEDs. In other words, as expected, sicker patients received more radiological investigation. This study did not evaluate outcomes associated with higher CED exposure. This is the first study in dialysis patients to evaluate cumulative radiation exposure. Other studies in other populations with chronic health conditions—such as hydrocephalus, pulmonary thromboembolic disease, and renal colic—have also shown high rates of cumulative radiation exposure, with an increase in CEDs from 2000–2001 to 2004–2005.⁶ In an analysis of claims data from UnitedHealthcare, Fazel et al.⁷ evaluated CEDs in more than 950,000 enrollees (aged 18–64) in the health plan between 2005 and 2007. This population was most likely healthier than the patients with ESRD in the study of Kinsella et al.⁵ Fazel et al. reported a much lower percentage of enrollees with annual effective doses > 20 mSv (2.1% for men and 1.9% for women) compared with the patients with ESRD (14%) in Kinsella and colleagues’ study. The increasing interest in cumulative radiation exposure from medical procedures is important because of clear links between such exposure and cancer and possibly CVD.⁸,⁹ In follow-up studies of patients with Hodgkin’s lymphoma, it was found that survivors were more likely than the general population to have experienced a myocardial infarction and congestive heart failure; it was also noted that mediastinal radiotherapy was one of the biggest risk factors for these conditions.¹⁰ Radiotherapy obviously uses much higher radiation doses than diagnostic studies; however, the risk of CVD with low-dose irradiation is unclear. Since CVD is the leading cause of death in patients on dialysis, it is intriguing to ponder whether exposure to radiation may also play a role in this outcome.

The study by Kinsella et al.⁵ brings up several important considerations. The first is that this study was performed in Ireland in an integrated national health system. The estimates for cumulative radiation exposure may be much higher in the United States, where patients sometimes go from hospital to hospital seeking care and do not carry their scans with them. In clinical practice, it is not unusual to see patients who were admitted in the previous month to a different hospital and had a CT scan but who then received another such scan because (i) patients’ medical records are hard to obtain, (ii) there is no immediate access to scan results, and (iii) physicians tend to fear litigation. It would be very interesting to see results from similar studies done in the United States and other countries with different healthcare-delivery systems. This study, pointing to the potential harm accruing to patients who receive high doses of radiation, serves as a further impetus for a national electronic medical record system that—after appropriate releases from patients—would facilitate the sharing of medical tests.

There are several limitations to the study by Kinsella et al.,⁵ including the fact that it is a single-center study with estimated CEDs based on radiological procedure, not actual exposure dose. The study does

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not actually show an association between radiation dose and cancer incidence or other outcomes but merely quantifies how much radiation exposure these 100 dialysis patients received over a 5-year period. The researchers did not have access to radiation exposure outside their institution and therefore probably underestimated the cumulative exposure.

In summary, the study by Kinsella et al. is an interesting first step in the epidemiology of radiation exposure in patients receiving dialysis. This analysis must be replicated in other cohorts before making recommendations about limiting radiation exposure, several questions must be answered:

1. Dialysis patients experience high mortality rates; do competing risks from underlying disease processes minimize the effects of radiation exposure in this population?
2. Is there an association between actual or estimated CEDs and cancer or CVD incidence and mortality in dialysis patients? This question might perhaps be answered by consulting available databases.
3. Is there an association between actual or estimated CEDs prior to transplantation and cancer or CVD incidence and mortality in patients with a kidney transplant who are receiving immune suppressants?
4. Are there simple ways to measure and track radiation exposure in dialysis patients, as we do in individuals with occupational exposures?

In summary, the study by Kinsella et al. opens the way for the evaluation of cumulative radiation exposure as a new, and importantly modifiable, risk factor in the dialysis population.

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REFERENCES