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Renal transplant recipients and complicated UTIs: a path toward next-generation care

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ABSTRACT

Renal transplant recipients face a heightened risk of complicated urinary tract infections (cUTIs) due to immunosuppression, anatomical changes, and recurrent urinary abnormalities. Traditional diagnostic methods, including standard urine cultures, are often insufficient in identifying fastidious organisms and multidrug-resistant (MDR) pathogens that contribute to recurrent infections. Emerging technologies, such as next-generation sequencing (NGS), offer a novel, culture-independent approach that improves pathogen detection, especially in cases involving polymicrobial infections or rare microbes. This article explores the role of NGS in addressing diagnostic limitations for renal transplant patients with cUTIs, highlighting its capacity to identify both bacterial and viral pathogens and their resistance profiles. The clinical relevance of NGS in enhancing treatment precision and improving graft outcomes is discussed, emphasizing the potential for reduced nephrotoxic effects from broad-spectrum antibiotics. As the incidence of antimicrobial resistance rises, advanced diagnostic solutions like NGS offer a promising path for optimizing post-transplant care and safeguarding graft function.

Mini-Review

Implication for health policy/practice/research/medical education:
Next-generation sequencing (NGS) offers diagnostic potential in managing complicated urinary tract infections (UTIs) in renal transplant recipients by enabling precise pathogen identification and resistance profiling. Integrating NGS into care protocols can improve graft preservation, reduce hospitalizations, and support antimicrobial stewardship. Policies should prioritize its adoption, while research explores cost-effectiveness and clinical outcomes. Medical education must emphasize NGS to prepare clinicians for advanced diagnostic approaches, fostering improved patient outcomes and innovative care solutions.

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Introduction

Renal transplant patients are especially vulnerable to complicated urinary tract infections (cUTIs), with incidence rates as high as 25% within the first-year post-transplant (1). The increased risk of infection in this population is due to several factors. These include chronic immunosuppressive therapy, anatomical changes from surgery, and possible pre-existing urinary tract issues. After a transplant, patients often experience reduced urinary flow and incomplete bladder emptying, which can lead to bacterial buildup and infection (2). Additionally, many transplant recipients have a history of recurrent UTIs or structural abnormalities, such as vesicoureteral reflux or ureteral stents, which further increase their risk of infection (3). Studies show the most common microbial culprits for UTI post-transplant are *Escherichia coli* (39%), *Enterococcus* spp. (16%), *Klebsiella* spp. (14%), *Staphylococcus* spp. (12%), *Enterobacter* spp. (8%), *Pseudomonas aeruginosa* (6%), and other bacterial species account for 5% of cases (4).

While common bacterial pathogens like *E. coli* dominate UTI microbial pathogenicity, there is a growing concern regarding the role of rare and emerging microbes in post-transplant UTIs, especially in the context of recurrent or treatment-refractory infections. Immunocompromised individuals—particularly renal transplant recipients—are at heightened risk for infections caused by atypical organisms such as *Candida* spp., *Nocardia*, *Corynebacterium urealyticum*, *Mycobacterium tuberculosis*, adenovirus, and polyomavirus BK (BKV) (5). These organisms can

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be challenging to diagnose with standard urine cultures due to their fastidious nature or low presence in urine samples. Notably, *Nocardia* and *M. tuberculosis* have been reported in renal transplant patients, particularly those with chronic immunosuppression. *Nocardia* species, commonly found in soil, can cause disseminated infections that affect the urinary tract, often manifesting as pyelonephritis or abscesses (6). *C. urealyticum*, although rare, has been increasingly recognized as an important uropathogen in transplant recipients due to its ability to form struvite stones and cause encrusted cystitis. This organism often exhibits multidrug resistance, making treatment challenging (7,8). Furthermore, viral pathogens such as BKV and adenovirus pose unique challenges in the post-transplant setting. BKV, in particular, has a well-documented association with hemorrhagic cystitis and polyomavirus-associated nephropathy, both of which can lead to significant morbidity and compromise graft function (9). Infections with adenovirus, though rare, can present as hemorrhagic cystitis or ureteritis in transplant recipients and are often resistant to standard antiviral therapies (10). Given the complexity and diversity of pathogens affecting renal transplant recipients, traditional diagnostic methods often fall short in identifying these complex infections, highlighting the need for more advanced techniques.

The role of next-generation sequencing (NGS) in the detection of these rare and difficult-to-culture pathogens has shown promise in the management of complex UTIs in renal transplant patients (11). Unlike traditional culture methods, NGS offers an unbiased, culture-independent approach to pathogen identification, allowing for the detection of bacteria, fungi, and viruses that may otherwise be missed with traditional laboratory diagnostics (12). NGS is particularly useful in cases of polymicrobial infections or infections caused by fastidious organisms, where standard cultures may yield false-negative results (13). For example, in cases where patients present with recurrent UTIs despite appropriate antibiotic therapy, NGS can identify biofilm-forming pathogens or low-abundance organisms, enabling more targeted diagnosis and treatment strategies (14). While common bacterial pathogens remain the predominant cause of UTIs in renal transplant recipients, there is an increasing recognition of the role of rare and emerging pathogens in this population. NGS has potential to aptly serve a critical role in the early detection and management of cUTIs, offering a broader, more sensitive diagnostic approach that is particularly valuable in immunocompromised patients (11).

Role of immunosuppression and host defense alteration

Immunosuppression in renal transplant recipients significantly alters both innate and adaptive immune responses, leading to atypical presentations and potentially severe outcomes of infections, including cUTIs. Specifically, calcineurin inhibitors, such as tacrolimus and cyclosporine, suppress T-cell receptor signaling pathways, resulting in diminished T-cell proliferation and cytokine production. This impairment compromises the host's ability to mount both primary and memory immune responses against common bacterial and viral pathogens (15). Mycophenolate mofetil, an antiproliferative agent, further disrupts lymphocyte proliferation by inhibiting guanine nucleotide synthesis, which affects both B and T cells, limiting antibody production and further weakening pathogen recognition and clearance (16). Corticosteroids, such as prednisone, exacerbate this immune suppression by inhibiting the nuclear factor kappa B (*NF-κB*) pathway, reducing the expression of pro-inflammatory cytokines like interleukin-*1* (*IL-1*), IL-6, and tumor necrosis factor alpha (TNF-α), which are critical in the activation and recruitment of innate immune cells (15).

These immunosuppressive regimens have a substantive impact on the host's ability to combat both opportunistic and common bacterial pathogens. In particular, infections caused by *E. coli*, *Klebsiella pneumoniae*, and *Enterococcus faecalis* are more likely to result in invasive disease due to the inability of immunosuppressed patients to mount an appropriate neutrophilic response. Neutrophils, which play a central role in the clearance of bacteria from the urinary tract, are often functionally impaired in transplant recipients. Studies show that neutrophil chemotaxis, phagocytosis, and intracellular killing are significantly diminished under immunosuppressive therapy, rendering patients more susceptible to pyelonephritis and urosepsis (17). Furthermore, macrophage function is also compromised, with reduced ability to engulf and destroy pathogens, leading to persistent bacteremia and systemic dissemination (15).

This altered immune landscape not only predisposes renal transplant patients to frequent infections but also complicates the diagnosis and management of UTIs. In immunocompetent individuals, UTIs typically manifest with dysuria, fever, and increased urinary frequency. However, in transplant recipients, these classical symptoms are often absent or muted due to the blunted inflammatory response. This atypical presentation makes early recognition of UTIs challenging and increases the risk of delayed treatment, which can result in rapid progression to upper tract infections and pyelonephritis (18). Pyelonephritis, especially if recurrent, has been linked to a decline in renal allograft function and an increased risk of graft loss (19).

The immunosuppressed state also alters the microbial landscape of UTIs, increasing the likelihood of infections caused by multidrug-resistant organisms (MDROs). The frequent use of prophylactic antibiotics in transplant recipients, further compounds this issue by selecting for resistant strains. As a result, infections with organisms such as extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* are increasingly common, complicating treatment and necessitating the

use of more toxic and less effective antibiotics (20). This highlights the need for precision diagnostics, such as NGS, which can provide rapid identification of uropathogens and their resistance profiles, enabling timely and appropriate therapeutic interventions. Early and accurate diagnosis, aided by advanced tools like NGS, is essential to prevent the progression to severe complications in immunosuppressed patients, including pyelonephritis, graft dysfunction and ultimately, graft loss.

Impact on graft function and long-term outcomes

The impact of cUTIs on graft function can be a clinical problem, as recurrent infections are closely linked to chronic allograft dysfunction and poor long-term outcomes in renal transplant recipients (3). One of the most severe complications, pyelonephritis, not only directly threatens the renal parenchyma but also triggers episodes of acute rejection, necessitating intensified immunosuppressive therapy. This creates a vicious cycle, where increased immunosuppression heightens susceptibility to opportunistic infections (21). Bacterial endotoxins, such as lipopolysaccharides from gram-negative organisms, initiate an inflammatory cascade that damages renal tubular cells and the graft itself. Cytokines like TNF-α and IL-6, released during infection, recruit immune cells to the infection site, causing collateral damage to the transplanted kidney (22). Over time, repeated pyelonephritis and UTIs contribute to fibrosis and scarring, gradually reducing nephron function and leading to chronic allograft nephropathy (23). Persistent infections exacerbate this inflammation, accelerating renal function decline. Therefore, early diagnosis and prompt treatment of cUTIs are crucial to preventing irreversible graft damage and preserving transplant longevity.

The implementation of prophylactic antibiotic regimens has been shown to reduce the incidence of cUTIs, particularly during the critical perioperative period when patients are most vulnerable to infections. Perioperative prophylaxis with antibiotics like trimethoprim-sulfamethoxazole (TMP-SMX) is effective in preventing both bacterial UTIs and *Pneumocystis jirovecii* pneumonia, another common post-transplant complication (24,25). Additionally, routine screening protocols, including regular urine cultures and urinalysis in asymptomatic patients, enable the early detection of bacteriuria before it progresses to symptomatic infections. However, the widespread use of antibiotics in renal transplant recipients presents a concerning dilemma. Over-reliance on antimicrobial agents increases the risk of developing antimicrobial resistance, particularly among common uropathogens like *E. coli* and *K. pneumoniae*, which are already showing high rates of resistance to first-line agents (20). The emergence of MDROs in this patient population complicates treatment strategies, often necessitating the use of broad-spectrum or toxic agents like carbapenems, which come with their own risks of nephrotoxicity. Balancing the need for effective infection control while minimizing the development of resistance is, therefore, a significant challenge in the long-term management of renal transplant patients.

Unlike traditional culture methods, which may fail to identify fastidious or MDROs contributing to recurrent infections, NGS provides a comprehensive analysis of both common and rare pathogens, along with their antimicrobial resistance profiles. This ability to rapidly identify the underlying cause of persistent infections is crucial for preventing the onset of severe complications like pyelonephritis, which can trigger acute rejection and initiate a cascade of inflammation leading to chronic allograft nephropathy. Moreover, by guiding more targeted antibiotic therapies, NGS reduces the need for broad-spectrum agents, thereby minimizing nephrotoxic effects and the risk of antimicrobial resistance. Incorporating NGS into the diagnostic and treatment protocols for cUTIs offers a proactive approach to safeguarding graft function and enhancing long-term outcomes

Multidrug-resistant uropathogens and antimicrobial stewardship

The rising prevalence of multidrug-resistant (MDR) uropathogens among renal transplant recipients presents challenges in the management of UTIs and underscores the urgent need for robust antimicrobial stewardship. MDR organisms, including ESBL-producing *E. coli* and carbapenem-resistant Enterobacteriaceae (CRE), are frequently isolated in transplant patients, particularly those with recurrent infections, prior exposure to broad-spectrum antibiotics, or extended hospital stays (26). The emergence of these pathogens limits the efficacy of empiric antibiotic regimens, often leading to therapeutic failure, prolonged hospitalizations, and increased mortality—especially infections caused by ESBL-producing organisms (27,28).

The challenge of treating MDR uropathogens in renal transplant patients is compounded by the limited availability of effective antibiotics. Many commonly used first-line agents, such as fluoroquinolones and trimethoprim-sulfamethoxazole, have significantly reduced efficacy against resistant organisms, necessitating the use of more potent agents like carbapenems. However, the over-reliance on carbapenems, particularly in institutions with a high burden of ESBL-producing or carbapenem-resistant pathogens, contributes to the growing global crisis of antimicrobial resistance (15). As a result, many experts advocate for carbapenem-sparing strategies, such as the use of beta-lactam/beta-lactamase inhibitors (e.g., ceftazidime-avibactam) or novel agents like cefiderocol, which have shown promise against resistant Gram-negative pathogens, including CRE (29).

Antimicrobial stewardship programs play a pivotal role in mitigating the spread of MDR organisms while ensuring that transplant patients receive effective

treatment. These programs aim to optimize antimicrobial selection based on local resistance patterns, reduce unnecessary exposure to broad-spectrum antibiotics, and improve clinical outcomes through targeted therapy (30). In renal transplant recipients, stewardship programs are particularly important due to the delicate balance between preventing infections and minimizing the risk of selecting for MDR pathogens. Regular surveillance of local resistance data (31,32) is essential for guiding empiric therapy, and in institutions with high rates of ESBL-producing organisms, early initiation of carbapenems or alternative agents may be necessary. However, these decisions must be carefully weighed against the risk of promoting further resistance, reinforcing the need for tailored antimicrobial protocols based on individualized risk factors and local epidemiology (30).

Prophylactic antibiotic use, while effective in reducing the incidence of post-transplant infections, also contributes to the selection of MDR organisms. Studies have shown that prolonged prophylaxis with agents such as TMP-SMX not only selects for resistant *E. coli* strains but may also increase the prevalence of resistant Gram-negative organisms in the gastrointestinal flora (33,34). This stresses the importance of regular review and adjustment of prophylaxis protocols based on evolving resistance patterns and the clinical status of the patient. Selective de-escalation of prophylactic antibiotics, especially in patients with stable graft function and no history of recurrent infections, can help reduce the selection pressure for MDR organisms, thereby preserving the efficacy of available antibiotics. The ultimate goal is to balance the need for effective infection control with the imperative to minimize the selection of resistant organisms, ensuring that transplant patients receive optimal care while safeguarding the utility of existing antimicrobials.

Preventive strategies and infection control

Table 1 presents a comprehensive overview of the key clinical and diagnostic insights for managing UTIs in renal transplant recipients. UTIs are a frequent complication in this population due to their immunocompromised state, with an incidence rate of up to 25% in the first-year post-transplant. The multifactorial risks include anatomical changes, pre-existing urinary tract abnormalities, and immunosuppressive therapies, which increase susceptibility to both common and rare pathogens. Traditional diagnostic methods, such as urine cultures, are often insufficient for timely detection, particularly in the context of fastidious organisms or biofilm-associated infections, leading to delays in appropriate treatment. Emerging technologies, such as NGS, offer significant

Table 1. Overview of risk factors, pathogens, and diagnostic challenges in renal transplant recipients with complicated UTIs

Category	Key information	Details/Insights	References
Population at risk	Renal transplant recipients	Patients on chronic immunosuppressive therapy are highly vulnerable to cUTIs.	(24,35)
Incidence of cUTIs	25% in the first-year post-transplant	Multifactorial risks include anatomical changes, immunosuppression, pre-existing urinary tract abnormalities, and recurrent UTIs.	(36,37)
Preoperative screening	Preoperative screening for asymptomatic bacteriuria in patients with recurrent UTIs or anatomical abnormalities	Reduces postoperative infection risk and improves graft outcomes.	(24)
Common pathogens	*Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp.	Prevalence of MDR strains complicates treatment.	(20,38)
Rare pathogens	*Candida* spp., *Nocardia*, *Corynebacterium urealyticum*, polyomavirus BK, adenovirus	Immunosuppressed patients are susceptible to rare pathogens that may not be detected by standard diagnostic methods.	(35,39)
Immunosuppressive drugs impact	Tacrolimus, cyclosporine, Mycophenolate mofetil, corticosteroids	These drugs impair immune function, increasing susceptibility to infection and complicating clinical presentations.	(20)
Prophylactic antimicrobial use	Tailored prophylactic regimens based on patient risk profiles	Regular follow-up cultures in high-risk individuals reduce the burden of UTIs.	(40)
Stent management	Prolonged ureteral stenting increases the risk of infections	Timely removal of stents and proper catheter care are essential for infection control.	(3)
Complications of cUTIs	Pyelonephritis, graft loss, chronic allograft nephropathy	Recurrent UTIs lead to inflammation, fibrosis, and loss of renal function, compromising graft survival.	(36,37)
Diagnostic delays	Traditional urine cultures require 48-72 hours to yield results	Delays initiation of appropriate treatment in critically ill renal transplant recipients, risking progression to pyelonephritis or urosepsis.	(11)

Table 1. Continued

Category	Key information	Details/Insights	References
Challenges with fastidious organisms	Pathogens like *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Corynebacterium urealyticum*	These organisms are often undetected in routine cultures due to slow growth or specific requirements, leading to delayed diagnosis and treatment.	(35,39)
Impact of prophylactic antibiotics	TMP-SMX prophylaxis for *Pneumocystis jirovecii*	Suppresses bacterial growth, causing false-negative cultures even in the presence of active infection, leading to delayed treatment and increased risk of graft dysfunction or sepsis.	(20,41)
Biofilm-associated infections	Pathogens like *Pseudomonas aeruginosa* and *Enterococcus faecalis* form biofilms	Biofilms are resistant to antibiotics and difficult to detect via standard cultures, causing chronic, recurrent infections.	(42,43)
Polymicrobial infections	Renal transplant recipients often present with polymicrobial infections	Standard cultures typically detect only the dominant organism, missing co-infections that worsen disease severity.	(38)
Advanced diagnostics	NGS	NGS detects pathogen DNA directly from clinical samples, including fastidious organisms and polymicrobial infections, and identifies antimicrobial resistance genes.	(13,44,45)
Antimicrobial resistance	ESBL-producing organisms and MDR strains	Widespread resistance complicates therapy, necessitating the use of more toxic agents such as carbapenems.	(15,46)
Treatment challenges	Standard cultures detect only planktonic bacteria and miss biofilm-associated infections	Biofilm-associated infections are difficult to treat due to antibiotic resistance, leading to recurrent UTIs.	(43)
Preventive strategies	Prophylactic antibiotics, regular urine screening, and ureteral stent management	Prophylactic use of TMP-SMX and timely removal of ureteral stents are essential in reducing UTI risks, though prolonged use can increase antimicrobial resistance.	(3,20)

cUTIs; complicated urinary tract infections; NGS, Next-generation sequencing; MDR, Multidrug-resistant; TMP-SMX, Trimethoprim-sulfamethoxazole.

advancements in identifying a broader range of pathogens and antimicrobial resistance genes, providing critical insights for personalized treatment strategies. Moreover, preventive measures, such as preoperative screening, prophylactic antibiotics, and timely management of ureteral stents, play a crucial role in reducing the burden of UTIs and improving graft outcomes.

To fully leverage these benefits, it is essential to collaborate with a laboratory that has developed NGS as a laboratory-developed test (47), as this ensures the technology is tailored specifically for complex UTIs in renal transplant recipients. Such collaboration facilitates more precise, targeted antibiotic therapies, reducing the reliance on broad-spectrum agents that carry nephrotoxic risks and contribute to antimicrobial resistance. Incorporating NGS into diagnostic and treatment protocols offers a proactive approach to safeguarding graft function and improving long-term outcomes, allowing for earlier intervention and optimized patient care.

Conclusion

Renal transplant recipients face significant risk from cUTIs due to the immunosuppressive therapy required to prevent graft rejection, anatomical changes, and recurrent infections. These patients are particularly vulnerable to both common and rare pathogens, many of which may be resistant to standard treatments. The use of NGS presents a critical advancement in diagnostic precision, allowing for rapid identification of fastidious, biofilm-forming, and polymicrobial infections, as well as antimicrobial resistance profiles. By improving early detection and enabling targeted therapy, NGS has the potential to significantly mitigate the risk of graft dysfunction and loss, offering a promising path forward in managing the complexities of infection in this vulnerable population. Future clinical strategies must integrate individualized care, antimicrobial stewardship, and continued innovations in diagnostic technology to preserve both graft function and patient quality of life.

Conflicts of interest

The author declares that he has no competing interests.

Ethical issues

Ethical issues, including but not limited to plagiarism, data fabrication, and double publication, have been thoroughly observed and adhered to by the author.

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