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Meta-Analysis

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Reduced graft survival in renal transplant patients with urinary tract infections – a meta-analysis

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ABSTRACT

INTRODUCTION. Renal transplant patients are prone to developing urinary tract infections (UTIs). However, the potential effect of a UTI on renal graft loss remains unclear.

METHODS. We systematically surveyed the literature for a potential association between UTI and graft loss. Articles were identified in online databases using a specific search string, followed by post selection for meta-analysis following four inclusion criteria: 1) a clear definition of UTI and recurrent UTI, 2) n > 200, 3) patient age > 16 years and 4) inclusion of data on graft loss. Data on UTI and graft loss were extracted from the included studies for calculation of a combined weighted odds ratio (OR) using the Mantel-Haenszel method. This review was conducted according to the PRISMA 2020 statement.

RESULTS. Unfortunately, only eight of 108 papers met the inclusion criteria. These studies reported between 276 and 2,368 patients, primarily male, aged around 50 years. The two-year incidence of overall UTI varied from 16.5% at a 27.5-month follow-up to 30.1% at a 24-month follow-up from transplantation. Seven papers were included in the OR analysis; two found an association between UTI and graft loss and five did not. However, in the meta-analysis, the weighted OR for all seven studies was 1.340 (95% confidence interval: 1.050-1.720).

CONCLUSIONS. Filtering the literature for a strict definition of UTI allowed us to establish an association between UTI and graft loss in renal transplant patients. However, further investigation and stronger studies using the Goldman criteria are needed to allow stratification for UTI severity and effect on graft loss.

KEY POINTS

- Urinary tract infections (UTIs) are common in renal transplant recipients.
- Our meta-analysis of seven studies found an association between UTI and graft loss.
- Poor definitions of UTI in the literature hinders determination of whether more severe infections further induce graft loss.
- More studies with substantial patient numbers and rigorous UTI definitions are needed.

Urinary tract infections (UTIs) are among the most common bacterial infections in humans. UTIs are usually confined to the urinary bladder, but may, in severe cases, ascend to the kidneys, causing pyelonephritis or disseminating into sepsis [1, 2]. In a general Danish population cohort, the one-year incidence of UTI was reported to be 3.4% and 76% of those affected were women [3]. Generally, otherwise healthy women are more prone to developing UTIs with an estimated lifetime incidence of 53%. Recurrent infections, defined as ≥ 3 UTIs for 12 months or ≥ 2 UTIs for six months [4, 5], are frequent and may reach as many as seven episodes during a six-month period [6, 7]. Comparatively, men are relatively protected against UTIs with a corresponding lifetime risk of 6.8% [8]. Despite UTIs being common in the general population, certain patient populations have an even higher UTI incidence. Generally, immunosuppression increases the infection risk, but renal transplant patients are particularly prone to contracting UTIs [9-11]. In renal recipients, the two-year incidence of UTIs is roughly similar for men and women with 11.6-13.1% in men and 3.4-18.5% in women, suggesting that men are less protected against UTIs after a renal transplant [12, 13]. Recurrent UTIs have a reported prevalence of 13-30% in renal transplant patients [11, 12, 14-19] and are of particular concern in terms of potential infection-induced damage of the renal graft due to the repeated challenge of the bacteria from the infection. Intuitively, one would expect severe UTIs to jeopardise graft function and it is therefore surprising that numerous studies were unable to detect an association between these parameters [13, 14, 16, 20-27]. We speculate that a lack of stringent UTI criteria may be diminishing an association between UTI and graft loss and hiding any positive correlation between infection severity and risk of graft loss. This review set out to investigate whether UTIs affect graft loss in kidney transplanted patients by analysing the literature on the subject.

METHODS

Selection of articles for analysis

From October 2020 to August 2023, articles for analysis were identified via the online search engines PubMed, Web of Science and Scopus using the search strings *kidney graft survival UTI* and *recurrent UTI kidney transplant*, and by screening the reference lists of the identified articles for relevant references. Articles that were deemed relevant based on their abstract were then read in full by one reviewer and subsequently kept for meta-analysis if they met the following criteria: 1) clear definitions of UTI and recurrent UTI, 2) the number of patients included exceeded 200, 3) all patients were over 16 years of age and 4) include data on graft survival. The inclusion criteria were established to ensure that 1) the definition of UTI was relevant and that the same definition was used in all patient groups, making them more comparable for analysis; 2) enough patients were included to perform meaningful statistical analysis with a cohort large enough to see outcomes with both UTI and graft loss in some patients, 3) data on children were not included and 4) data on the outcome we wished to examine (graft loss) were included. We chose to eliminate children from this review since the incidence of UTI is described to be considerably higher in child recipients (24-75%) and we did not want this to skew any incidence we might find in adults [28-33]. Reviews and case reports were not included as relevant articles for analysis, since we sought original data on UTI and graft loss that could be used in a meta-analysis. Both inclusion and exclusion criteria were determined before the literature search was initiated to prevent selection bias.

Definition of urinary tract infection and recurrent urinary tract infection

We used the 2019 Goldman guidelines classification of UTIs in renal transplant recipients, divided into the categories of *acute simple cystitis* and *acute pyelonephritis/complicated UTI* [4]. Recurrent UTI was defined as ≥ 3 UTIs for 12 months or ≥ 2 UTIs for six months [4, 5]. Only studies following these definitions of UTI in renal transplant patients were included. Asymptomatic bacteriuria, defined as presence of bacteria in the urine without relevant symptoms [4, 34], was not included as a definition of UTI since it is common in renal transplant

patients and does not warrant treatment or screening as it does not affect the risk of UTI, graft loss or death [19, 27, 35-38]. All studies with a UTI definition including the definition of asymptomatic bacteriuria were therefore excluded.

Statistics

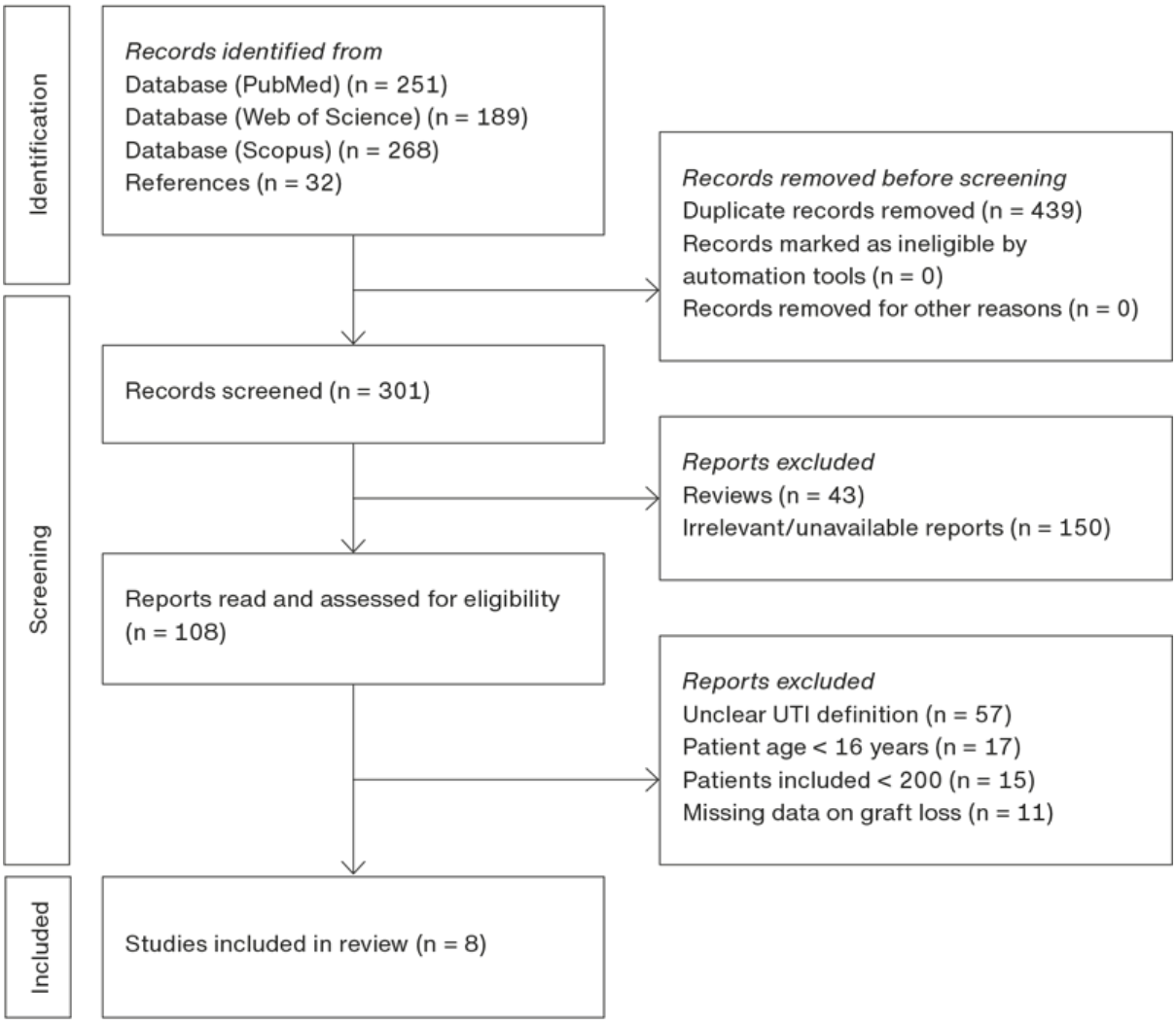
Statistical analysis was performed in GraphPad Prism version 10.0.0 for Windows (GraphPad Software, La Jolla, CA, USA) and Microsoft Excel, using a template expanded upon from EpiBasic version 5.0 (developed by Svend Juul and Morten Frydenberg, maintained by Stefan Hansen). Information on number of patients with graft loss and number of patients with UTI (according to our definition) was extracted from included articles, and an odds ratio (OR) with a 95% confidence interval (95% CI) was calculated. Only patients with information on both UTI and graft loss were included in our analysis. Finally, a weighted OR was calculated for all included articles using the Mantel-Haenszel method [39]. Data are presented as mean ± standard deviation or OR with 95% CI unless otherwise specified. This review was conducted according to the PRISMA 2020 statement [40].

RESULTS

Patient characteristics

Out of 301 articles, 108 were read in full. Among these, only eight were included for analysis based on outlined criteria (**Figure 1**). All included studies were retrospective, published from 2006 to 2023, except one which was a longitudinal observational study [24]. **Table 1** summarises the patient characteristics in the articles. Overall, the studies included between 276 and 2,368 patients, primarily male, with an overall age around 50 years. The nature of end stage renal disease and primary indication for a renal transplant were not included in three of the studies (marked *Unknown* in Table 1), and information on surgical techniques, including use of post-surgical catheters, was generally scarce. Use of double J stents for a varying number of weeks after transplantation was often considered standard procedure and five of the included studies described use of these for most patients without detailing the number of patients in question [12, 13, 15, 21, 24]. The remaining three articles did not include any information on stent use [20, 41, 42].

FIGURE 1 Flow chart for studies included in review.



UTI = urinary tract infection.

TABLE 1 Patient characteristics in the eight studies.

	Kamath et al., 2006 [12]	Ariza-Heredia et al., 2014 [15]	Bodro et al, 2015 [20]	Brakemeier et al., 2017 [21]	Freire et al., 2018 [41]	Sánchez et al., 2020 [13]	Brune et al., 2022 [24]	Halskov et al., 2023 [42]
Type of study	Retro	Retro	Retro	Retro	Retro	Retro	Longi	Retro
Patients, n	1,022	301	867	684	652	276	2,368	571
Age, yrs								
Mean	33.78[a]	56.7		50.32[a]		45.17[a]		
Median			50.80[a]		49		54.84[a]	52.00
Female gender, %	19.28	41.20	40.02	42.11	54.91	39.13	35.81	37.30
Donor, %								
Living	95.79	84.72	23.64	-	20.40	6.52	40.79	38.53
Deceased	4.21	15.28	76.36	-	79.60	93.48	59.21	61.47
End stage renal disease, n								
Diabetic nephropathy		60			159	6	197	50
Hypertension		54				58		42
Polycystic kidney disease		47				14	456	97
Focal segmental glomerulosclerosis		28						
Glomerulonephritis		22			230	47		136
Other		66				50	1,715	100
Unknown	1,022	24	867	684	263	101		145
UTI/1,000 renal transplant patients, n	165.36	182.72	212.23	190.06	273.01	300.72	258.02	85.41[c]
Type of UTI, n								
Asymptomatic bacteriuria	0	46	228	172	37	0	353	
Acute simple cystitis	0	32	58		88	0		
Acute pyelonephritis/complicated UTI	169	23	126		90	83		
UTI not subdivided	0	0	0	130	0	0	611	49[c]
R-UTI/1,000 renal transplant patients, n	38.16	46.51	63.44	97.95	56.75	126.81	65.46	180.39
R-UTI out of total UTI, %	23.08	25.45	19.89	51.54	20.79	42.17	25.37	-
Graft loss/1,000 renal transplant patients, n	67.51	39.87	43.83	131.58	87.65[b]	54.35	31.25	84.06
Graft loss caused by UTI, %	23.21	-	44.74	30	36.36	33.33	18.92	20.83[d]
Patient mortality/1,000 renal transplant patients, n	60.67	13.29	29.99	96.49	155.38[b]	43.48	20.69	59.54
Mortality caused by UTI, %	50	-	30.77	18.18	46.15	25	34.69	-

Longi = longitudinal study; R = recurrent; Retro = retrospective study; UTI = urinary tract infection.
a) Calculated from the data provided in the article.
b) n = 251.
c) Only in first the 30 days after transplantation
d) Due to R-UTI, not UTI in general.

Urinary tract infections

UTI incidence among renal transplant patients varied from 16.5% 27.5 months to almost doubling at 30.1% 24 months after transplantation (**Table 2**). Most studies reported UTI incidences for the entire follow-up period from transplantation, which varied greatly from ten days to 10.5 years [12, 15, 21, 41]. However, four articles examined UTI incidence at the following fixed timepoints: 30 days, one year and two years post transplantation, respectively [13, 20, 24, 42]. UTIs could be divided into the categories *acute simple cystitis* or *acute pyelonephritis/complicated UTI* in five of the studies, whereas the last three studies pooled patients with symptoms fitting both categories [21, 24, 42] (marked *UTI not subdivided* in Table 1). UTIs recurred in 3.8-18.0% of renal transplant patients and accounted for 19.9-51.5% of total UTIs during the follow-up periods [12, 20, 21, 42]. Generally, 25-50% of the renal transplant patients who developed a UTI would end up having recurring UTIs [12, 13, 15, 21, 24].

TABLE 2 Urinary tract infection (UTI) incidence by follow-up period. Cumulative incidence of UTIs in the study population at one month, three months, six months, one year, two years and for the entire follow-up period of the study. Follow-up period is presented as the median except where otherwise specified. Follow-up times presented as days or years in the articles were converted into months.

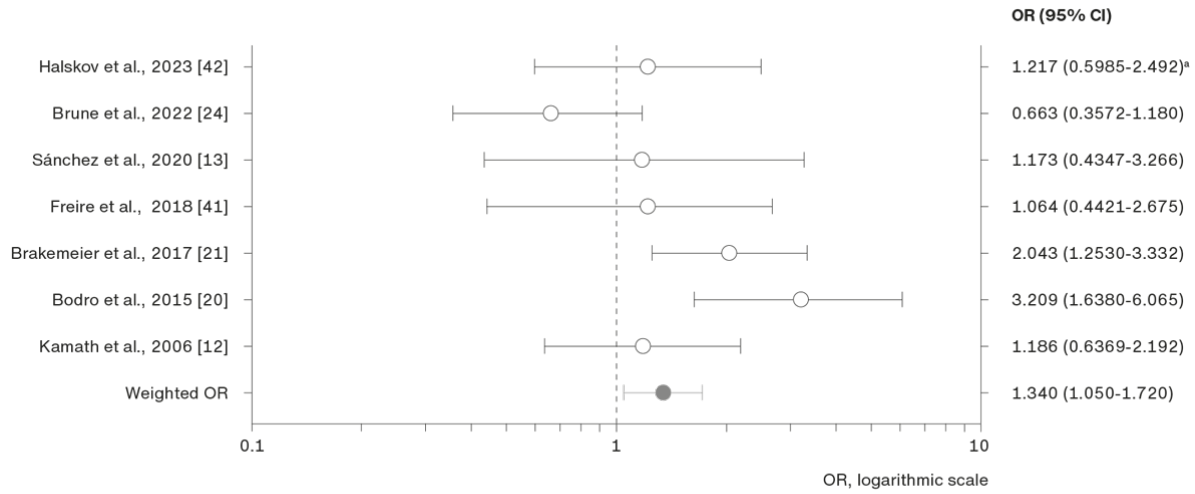
Reference	1 month, %	3 months, %	6 months, %	1 year, %	2 years, %	Follow-up, %	Median follow-up, months
Ariza-Heredia et al., 2014 [15]						18.3	10.0
Bodro et al, 2015 [20]				21.2		21.2	17.8
Kamath et al., 2006 [12]		11.2				16.5	27.5[a]
Sánchez et al., 2020 [13]					30.1	30.1	24.0[b]
Brakemeier et al., 2017 [21]						19.0	60.0[b]
Freire et al., 2018 [41]	9.4		25.6			27.3	22.2
Brune et al., 2022 [24]				25.8		25.8	12.0
Halskov et al., 2023 [42]	8.6					18.0[c]	44.0

a) Average calculated of 2 medians of 25 and 30 months.
b) Follow-up period specified as max number of months.
c) Only recurrent UTI was calculated in this study.

Graft loss

For this study, new calculations were made of ORs between graft loss and UTI in renal transplant patients. These calculations were based on the strict definition of UTI, excluding asymptomatic bacteriuria, and on the available data in the articles. One study included data on graft loss but did not disclose whether patients with graft loss had experienced UTI or not, and thus could not be included in the OR calculations [15]. We found that for two papers, an association existed between UTI and graft loss; Brakemeier et al. with an odds ratio (OR) = 2.043 (95% CI: 1.253-3.332) and Bodro et al. OR = 3.209 (95% CI: 1.638-6.065) (**Figure 2**). The remaining five studies showed no correlation between UTI and graft loss. Next, a weighted OR was calculated from all seven papers using the Mantel-Haenszel method. Interestingly, we found a significant weighted OR of 1.340 (95% CI: 1.050-1.720), indicating an association between UTI and graft loss. Unfortunately, we were unable to investigate whether the degree of infection impacted the risk of graft loss. Only Bodro et al. provided information on both *acute simple cystitis* and *acute pyelonephritis/complicated UTI* and number of patients suffering from graft loss in either UTI subcategory. When conducting analyses by UTI subgroup, we found an OR = 1.719 (95% CI: 0.526-5.322) for *acute simple cystitis* and an OR = 3.940 (95% CI: 1.920-7.866) for *acute pyelonephritis/complicated UTI*, suggesting an increased risk of graft loss with more severe UTI. This runs counter to Kamath et al. and Sánchez et al. who both exclusively reported UTIs belonging to the *acute pyelonephritis/complicated UTI* subgroup; where we found no association with graft loss. It should also be noted that Halskov et al. only investigated the association between recurrent UTIs and risk of graft loss, whereas the other studies studied any UTI occurrence [42].

FIGURE 2 Odds ratio for graft loss in renal transplant patients with urinary tract infection.



CI = confidence interval; OR = odds ratio; UTI = urinary tract infection.
a) Only recurrent UTIs were included in this calculation.

All eight studies included in this review reported their own analyses of the correlation between UTI and graft failure or graft loss. Four studies, however, included patients with asymptomatic bacteriuria in their UTI calculations and some had patients divided into different groups based on other factors. This may explain any differences between the results in the original paper and in the present review. Bodro et al. [20] found that *acute pyelonephritis/complicated UTI* negatively impacted graft survival (log-rank test < 0.001), which is in line with our analysis. In contrast, Brakemeier et al. [21] did not find that graft survival was impacted by UTI (p = 0.18), which contrasts with the results we found based on their data (Figure 2). Sánchez et al. [13] found a larger tendency for *acute pyelonephritis/complicated UTI* to increase loss of graft function in their analysis than we did (reported OR = 2.5 (95% CI: 0.9-7.0); p = 0.84). Kamath et al. [12] found that a complicated UTI did not in itself lead to increased graft loss, but it was associated with bacteraemia (p < 0.001) and bacteraemia was associated with graft loss (hazard ratio (HR) = 1.848 (95% CI: 1.245-2.743); p = 0.002). The last four studies found that neither UTI nor recurrent UTI was associated with graft loss; Ariza-Heredia et al. [15] presented a HR = 0.82 (95% CI: 0.17-3.91) for UTI and graft loss, whereas Freire et al. [41] reported a calculated HR = 1.06 (95% CI: 0.44-2.51); p = 0.90; for UTI and HR = 0.30 (95% CI: 0.06-1.47); p = 0.17; for recurrent UTI in univariate analysis. Halskov et al. [42] found no association between recurrent UTI and graft loss using a risk time-dependent Cox regression with delayed entry and death as a competing risk, whereas Brune et al. found no association between any degree of UTI and graft loss (p = 0.13), but did find decreased levels of estimated glomerular filtration rate (eGFR) in patients with recurrent UTIs compared to patients both with and without UTIs one year post-transplant, along with a negative association between recurrent UTIs and long-term death-censored graft survival [24]. In summary, only one of the eight studies reported an association between UTI and graft loss, whereas we found an association in two of seven studies and an overall positive association in the weighted analysis. The strict UTI criteria used for this analysis resulted in the exclusion of many articles, including some that found a positive association, which we believe strengthens our results.

DISCUSSION

General findings and limitations of the study

UTIs affect renal transplant patients more frequently than the general population. In a general Danish population, the one-year incidence of UTIs was reported as 3.4% and the five-year incidence as 7.9% [3]. In

contrast, the studies included in this article yielded a one-year incidence of UTIs in renal transplant patients of 21.2-25.8% and a five-year incidence of 19.0% (Table 2); both of these figures are considerably higher than those of the general population [20, 21, 24]. UTIs are usually considered benign and easily treatable infections confined to the bladder. However, a potential exists for an increased risk of dissemination during immunosuppression, which may threaten a recently transplanted kidney, ultimately resulting in graft loss. Based on data analysed from seven articles on the subject and a total number of 6,039 patients, we found a weighted OR of 1.340 (95% CI: 1.050-1.720), indicating that development of UTI did, indeed, increase the risk of graft loss. Our analysis, however, is not without limitations. We were able to include only eight out of 108 relevant papers (7.41%) on the topic and only seven could be included in our statistical analysis based on our inclusion criteria. Furthermore, we had to exclude 702 patients from the included studies due to lack of data on UTI and graft loss [15, 21]. The weighted OR therefore reflects a low number of both articles and patients included for analysis compared to what can otherwise be found in the literature.

The included studies were all retrospective except Brune et al. which was a longitudinal observational study. This may challenge the uniformity of the data collected at the time of transplantation and in the follow-up period. Substantial variation was observed between the studies, which made direct comparison difficult. The median follow-up period of patients varied from ten months to 44 months from time of transplantation [15, 42] and many studies had a longer total follow-up period. The cumulative incidence of UTIs will increase over time, meaning that studies with longer follow-up periods will inevitably present a higher cumulative incidence of UTIs. Furthermore, information on use of immunosuppressive treatment, surgical techniques and reporting on risk factors for UTI in renal transplant patients varied greatly between the included studies, making it difficult to discern any association between these factors and UTI and graft loss. Six of the included studies reported risk factors for UTI in renal transplant patients, but often found conflicting results; in four papers, extended use of a double J stent and female gender, respectively, were considered risk factors for development of UTI, whereas two papers found that they were not, and only half of the papers found that urological abnormalities, delayed graft function and CMV infection were risk factors for UTI [12, 13, 15, 20, 41, 42].

Issues with urinary tract infection definitions for renal transplant patients

The variety in studies on UTI and graft loss in renal transplant patients is what led us to define our inclusion criteria. The four criteria were established to ensure inclusion of more comparable studies. One of our inclusion criteria was a clear definition of UTI and recurrent UTI, from which we excluded asymptomatic bacteriuria. Inclusion of asymptomatic bacteriuria in UTI statistics may lead to overestimation of UTI prevalence in renal transplant patients and an underestimation of the effects of UTIs on graft function. Five of the papers included had data on asymptomatic bacteriuria, which, if grouped with UTIs, were excluded from our analysis [15, 20, 21, 24, 41]. Many studies included asymptomatic bacteriuria in their UTI definition, and the majority of the papers read for this review were excluded due to a lack of a precise UTI definition (57/108) [43-55]. Moreover, we were unable to distinguish the degree of infection according to the categories proposed by Goldman et al. [4] in comparison to graft loss. Among the seven papers included for analysis, only two had data stratified for *acute pyelonephritis/complicated UTI* and graft loss, whereas the remaining five reported on a mix of UTI presentations and graft loss. We would assume that development of pyelonephritis, which directly affects the kidney, or urosepsis, which leads to more severe illness, would increase the risk of graft loss in renal transplant patients, but we were unable to discern this effect based on the current literature; mainly due to lacking UTI definitions. Most current general UTI definition guidelines are based on the concept of complicated and uncomplicated UTIs introduced with the Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines [56]. The term complicated UTI is very broad, including patient risk factors and pathogen resistance, etc., which in general definitions means that immunosuppressed

transplant patients always have complicated UTIs. Therefore, we used the Goldman et al. 2019 UTI classification guidelines for renal transplant patients [4]. In the general definition, complicated UTI embraces a very heterogeneous group, where cystitis in a man would be comparable to pyelonephritis in a postmenopausal woman [56]. In a 2011 review, Johansen et al. proposed using a classification system which accounts for the clinical presentation of UTI, host risk factors, pathogens and therapeutic options, yielding a much more detailed division of the different UTI presentations, which is also applicable to renal transplant patients [56]. However, this classification system is not widely used in the literature. Using a strict definition of UTI may also lead to a decrease in the observed variance in UTI incidence among renal transplant patients.

Antibiotic treatment and risk of pathogen resistance in renal transplant patients

The incidence of UTIs is higher among renal transplant patients than in the general population. Renal transplant patients are immunosuppressed, which may explain part of the susceptibility to UTIs among an increased risk of general infections. Antibiotic prophylactic treatment is therefore a cornerstone in transplant care. The preferred prophylaxis against *Pneumocystis jirovecii* pneumonia in renal transplant patients is trimethoprim-sulfamethoxazole, which has also been described as having a protective effect against bacteriuria and bacteraemia. However, it remains unclear if it prevents graft loss or reduces mortality [16, 57]. The most common treatment period is six months, though some studies reported treatment for the first year after transplantation and others provided lifelong treatment [11, 16, 21, 41]. Pathogen resistance to common antibiotics is already high in renal transplant patients, and prolonged antibiotic treatment carries an additional risk of bacterial resistance [58, 59]. Korayem et al. found that in adult renal recipients one year after transplant, pathogen resistance against trimethoprim-sulfamethoxazole was as high as 88% for first-time UTI [60]. This was supported by Di Cocco et al., who found bacterial resistance against trimethoprim-sulfamethoxazole at 70.8% in renal transplant patients with UTIs [61]. A high prevalence of resistant pathogens and long antibiotic treatment periods may lead to a future increase in the already high incidence of both singular and recurrent UTIs in renal transplant patients.

CONCLUSIONS

The effect of UTIs on renal transplant patients depends on a complex interplay of a wide range of factors. Information about all these factors is rarely included in the papers published in this area, which makes comparisons between articles and therefore meta-analysis difficult. Comparisons are further complicated by varying UTI definitions. The analysis of the seven papers included in this review found that UTI increased graft loss in renal transplant patients. However, poor definitions of UTI hindered our ability to determine whether more severe infections further induce graft loss. It is critical to discern whether UTIs impact graft and patient survival in renal transplant patients, especially given that this patient group has both a high incidence of UTIs and use of antibiotics, putting them at increased risk of infection with a resistant pathogen. Therefore, we need more prospective studies with substantial patient numbers and rigorous UTI definitions.

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