Overview on urinary tract infection, bacterial agents, and antibiotic resistance pattern in renal transplant recipients

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Background: Urinary tract infection (UTI) is a mainly common infection in kidney transplant recipients. This study decided to investigate UTI, bacterial agents, and antibiotic resistance pattern in kidney transplant recipients from Iran. Materials and Methods: Search process was conducted for UTI, bacterial agents, and antibiotic resistance pattern in kidney transplant recipients from Iran via electronic databases (Scopus, PubMed, Web of Science, etc.) with Mesh terms in either Persian and English languages without limited time to May 31, 2020. Data were analyzed by comprehensive meta-analysis software. Results: The combined prevalence of UTI in renal transplant recipients was reported by 31.1%. The combined prevalence of Gram-negative bacteria was 69%. The most common pathogens among Gram negatives were E. coli followed by Klebsiella pneumoniae with frequency 43.4% and 13%, respectively. Subgroup analysis for Gram-positive bacteria showed the combined prevalence of 31%. The most common microorganism among Gram positives belonged to coagulase-negative Staphylococci and Enterococci with a prevalence of 10.2% and 9%, respectively. Subgroup meta-analysis of antibiotic resistance for Gram-negative showed the most resistance to cephalaxin followed by carbencillin with a prevalence of 89.1% and 87.3%, respectively. Conclusion: Our review showed a noticeable rate of UTI (31.1%) among renal transplant recipients in Iran and a high prevalence of Gram-negative (69%) and Gram-positive (13%) microorganisms. A high resistance rate was seen against almost all antibiotics used for the treatment of UTI. Therefore, empirical prescription of antibiotics should be avoided, and it should be based on data obtained from antibiogram tests.

Key words: Antibiotic resistance, bacteriuria, kidney grafting, renal transplantation, urinary tract infection

INTRODUCTION

As we know kidney transplantation despite the high cost is clinically effective treatment for the end-step renal disorder,¹ nowadays, it is possible with a profitable kidney transplant increases quality of life in patients and decreases mortality.² Posttransplant complications are produced such as dialysis and the altered anatomy of the urogenital tract.²,³ The main cause of mortality and morbidity in kidney transplant recipients is bacterial infection.⁴ Urinary tract infection (UTI) is mainly a common infection in kidney transplant recipients.⁵,⁶ In original, bacteriuria categorizes into two types: asymptomatic bacteriuria (ASB) and symptomatic UTI.⁷ ASB is defined as the growth of bacteria with >10⁵ CFU/mL, wherein the patients do not have any symptoms of infection.⁸ Based on recent reports, treatment of ASB might not be required and there was no adverse side effect on transplant outcomes.

UTI is defined by the overgrowth of bacteria >10⁶ CFU/mL from patients’ urine samples alongside with symptoms including dysuria, suprapubic, flank or allograft

Access this article online

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_286_18

How to cite this article: Zhang X, Gao H, Fu J, Lin F, Khaledi A. Overview on urinary tract infection, bacterial agents, and antibiotic resistance pattern in renal transplant recipients. J Res Med Sci 2021;26:26.
pain, fever, or chills. There are a lot of risk factors for susceptibility to UTI such as acute rejection, female sex, older age, longer durations with a urinary catheter, episodes, and receiving a kidney from a deceased donor.

Organisms that cause UTI post renal transplantation are bacterial, fungal, viral, parasitic, or mycoplasmal. The order of bacterial UTI pathogens in transplant recipients is comparable to that in the nontransplantation population: Gram-negative bacteria are responsible for over 70% of UTI cases. The high frequent bacterial agents causing UTI are Escherichia coli, K. pneumoniae, Enterococcus sp., Enterobacter, Pseudomonas aeruginosa, and Proteus mirabilis.

In some cases, microorganisms that are not problematic in immunocompromised patients have been involved in posttransplantation UTI. This possibly due to immunosuppressant drugs used in these patients, which accelerates bacterial–urothelial adherence. Hence, resistant bacterial strains can cause the problem to patients.

UTI via the inflammatory cytokine response, free-radical production, CMV reactivation, precipitation of rejection, and pyelonephritis-induced renal scarring can impair graft function. It is debatable that how much UTI can affect transplant function and patient survival. However, many retrospective studies have found no significant association between UTI, transplantation, and patient survival.

Concerning the importance of bacterial UTI in renal transplant recipients, and increasing their antibiotic resistance, this study decided to evaluate UTI, bacterial agents, and antibiotic resistance pattern in renal transplant recipients from Iran through systematic review and meta-analysis.

MATERIALS AND METHODS

Strategy search
Prisma protocol (PRISMA, http://www.prisma-statement.org) was used for searching UTI, the prevalence of microorganisms, and antibiotic resistance pattern in kidney transplant recipients from Iran in both international and national online electronic databases such as Scopus, PubMed, Cochrane Library, Web of Sciences, Iranmedex (www.irandmedex.com), Magiran (www.magiran.com), and Scientific Information Database (www.sid.ir). Mesh terms and text words were urinary tract infection, UTI, kidney transplant, renal transplant, post kidney transplant, antimicrobial drug resistance, and antibiotic resistance pattern. Published studies were searched without time limitation until May 31, 2020.

Inclusion and exclusion criteria
Cross-sectional, cohort, and case–control studies addressing the prevalence of UTI, bacterial pathogens, and antibiotic resistance pattern in renal transplant recipients were enrolled in the current systematic review and meta-analysis. Different types of review articles (systematic, narrative review, and meta-analysis), studies with missed data, conferences, meetings, abstracts, and studies published in languages other than English or Persian were excluded. Studies introduced other than kidney transplants were excluded from the study. Of note, two reviewers conducted searches independently.

Assessment of selection bias and quality of selected studies
To achieve this purpose, the criteria given in Critical Appraisal Skills Programmed checklists (www.casp-UK) were used. Hence, 10 questions were asked and if the answer was yes, one point would be considered, and if the answer was no, or if there was any doubt, the score would be 0. At the end, according to the scoring system, strong studies scored above 8, average studies between 5 and 8, and weak studies obtained scores below 4 (file 1).

Data extraction
By use of extract forms, the following data extracted: the first author’s name, time of the study, publication year, settings, sample size, prevalence of UTI, Genus, and mean age.

Statistical analysis
Comprehensive meta-analysis software was used for data analysis. The prevalence of UTI, antibiotic resistance, and bacterial agents was calculated by 95% confidence intervals. Due to the existence of heterogeneity among studies, a random effects model was used. I² and the Q-statistic tests were used for the assessment of heterogeneity among studies included in the present review. P < 0.05 of Q-test and I² test >50% was considered statistically significant.

In this study, we evaluated the publication bias visually through the Funnel plot. If the distribution of articles is evenly placed inside the funnel, it indicates that there is no publication bias, and if they placed outside the funnel or there is a heterogeneous and unbalanced distribution inside the funnel, it indicates the presence of bias in the study publication. In addition to the Funnel plot, the statistical Egger’s linear regression test was used to further investigate publication bias. According to this test, if the P < 0.05, it indicates the existence of publication bias; otherwise, if it is greater than this value, it indicates the absence of publication bias in the studies included. Finally, subgroup analysis was made for bacterial species and antibiotic resistance.
RESULTS

Selection study and features
The selection process is shown in Figure 1. Totally, 819 articles potentially were identified, 18 out of which met inclusion criteria for enrollment in the present systematic review and meta-analysis. Most studies were from Tehran (N = 7), followed by Mashhad (N = 4). Patients had mean age of 5–87 years [Table 1]. Most studies had cross-sectional design and 2 studies were case control.

Overall effects
According to the findings obtained from the systematic review and meta-analysis which are shown in Figure 2 and Table 2, the combined prevalence of UTI in renal transplant recipients was reported by 31.1% (95% CI: 24.1–39.1), Z = 4.4, Q = 538, I² = 96.8.

Publication bias
Regarding the Funnel plot [Figure 3], because there was a heterogeneous and unbalanced distribution inside the funnel, and studies placed outside the funnel, it indicated the presence of bias in the publication. To further evaluation, the statistical Egger’s Linear Regression Test was used; however, the findings showed no publication bias in the studies included, because P = 0.29 [Table 2].

Subgroup analysis for Gram-negative bacteria
As listed in Table 2, subgroup analysis showed that the combined prevalence of Gram-negative bacteria was 69% (95% CI: 23.6–99.5), Z = 11, Q = 201 and I² = 94. The most common pathogens among Gram negatives were E. coli followed by K. pneumoniae with frequency 43.4% (95% CI: 38.4–50.1), and 13% (95% CI: 7–19.9), respectively. Furthermore, the least rate belonged to Acinetobacter baumannii with a prevalence of 3% (95% CI: 1.4–5.8).

Subgroup analysis for Gram-positive bacteria
Subgroup analysis for Gram-positive bacteria showed the combined prevalence of 31% (95% CI: 12.2–48.4), Z = 5.7, Q = 65.1 and I² = 90.8. The highest predominant microorganism among Gram positives belonged to coagulase-negative staphylococci (CoNS) and Enterococci with a prevalence of 10.2% (95% CI: 5.4–18.2) and 9% (95% CI: 4-3.9), respectively.

Subgroup analysis for antibiotic resistance
Subgroup meta-analysis of antibiotic resistance for Gram-negative bacteria showed the most resistance to cephalaxin followed by carbenicillin and ceftazidime with the prevalence of 89.1% (58.8, 102), 87.3% (58.8, 99.3), and 86.3% (47.4, 88.6), respectively. The least resistance was observed against imipenem with a resistance rate of 13% [Table 3]. Furthermore, based on the data summarized in Table 4, the highest resistance of Gram-positive bacteria reported against amoxicillin and cephalaxin with a resistance rate of 79% (38.1,96) and 74% (33.4,98.91), respectively. The effective antibiotic for treatment of Gram-positive bacteria was reported Polymyxin B (10.6%). Findings of antibiotic resistance for E. coli in Table 5 showed the highest resistance against cotrimoxazole and nalidixic acid with a resistance rate of 74.1% and 70%, respectively. As well, the best antibiotics for treatment of UTI caused by E. coli were reported imipenem and nitrofurantoin with resistance rates of 13.2% and 19%, respectively.

DISCUSSION
In total, UTI is considered as the most common infection and the most possible site of infection that leads to hospitalization of patients with kidney transplantation.[20] The prevalence of UTI in kidney transplant recipients is similar in both developed and developing countries.[5] The prevalence of posttransplant UTI in the kidney transplant recipients varies between 12% and 75%.[21] Of course, in developing countries, this rate may be higher due to epidemiological exposure and lower standards of hygiene.[22] A meta-analysis conducted in 2016 showed that the USA had a significantly higher prevalence of UTIs than European countries (41% vs. 33%).[9] In the present systematic review and meta-analysis, the combined prevalence of UTI in renal transplant recipients
was reported by 31.1%. The combined prevalence of Gram-negative bacteria was 69%. The most common pathogens among Gram negatives were *E. coli* followed by *K. pneumoniae* with frequency 43.4% and 13%, respectively. Furthermore, the least rate belonged to *A. baumannii* with prevalence of 3%. Furthermore, subgroup analysis for Gram-positive bacteria showed the combined prevalence of 31%. The highest predominant microorganism among Gram-positives belonged to CoNS and Enterococci with prevalence 10.2% and 9%, respectively.

The prevalence in Iranian studies included in the current review varied from 4.5% to 67.5%. Our result (31.1% UTI's prevalence) was in line with our studies conducted in other parts of the world such as Turkey, Pakistan, Australia, and the USA. Similar findings in other studies support the concept that UTI still is the most predominant infection postrenal transplantation. The difference in the prevalence of UTI (4.5%–67.5%) in studies included in the present review and other studies from worldwide likely attributed to differences in the definition of UTI, the interval of follow-up, antibiotic prophylaxis used posttransplantation, and inherent differences of the person features among diverse countries.

Similar to our study, others reported the Gram-negative bacteria as the most common organisms isolated from UTI samples of both the nontransplant and transplant...
patients with the prevalence of 90%. We reported E. coli followed by K. pneumonia as the most prevalent Gram-negative bacteria, as other reports confirm it. In line to our study, a study conducted by Senger et al. in 2003, Enterococcus, Staphylococcus, and Streptococcus reported as the highest frequent bacteria. Similarly, Al Midani et al. from the UK, Camargo et al. from Brazil, Bodro et al. from Spain, reported E. coli and K. pneumonia as the most frequent Gram-negative bacteria. As well, Edirigweera et al. from Sri Lanka reported CoNS as the most Gram+, Wang et al. from Taiwan, Chuang et al. from the USA reported Enterococcus species as the most common Gram-positive bacteria recovered from UTI samples of kidney transplant recipients. All studies mentioned are inconsistent with our findings.

Several studies have confirmed that UTI is related to transplant function failure, particularly in the early posttransplant episode, but others have not reported such association. Additionally, another one found no profit of antibiotic prophylaxis on transplant function in the first 6 months post transplantation. Recently, some studies have shown a rising prevalence of infections caused by Multi-drug-resistant (MDR) strains in both immunocompetent and immunocompromised patients. As several reports presented a high rate of infections are

Table 2: Subgroup meta-analysis for both Gram-positive and negative bacteria

| Subgroups | Number of study | Random model | Heterogeneity test | Egger’s test |
|-----------|----------------|--------------|--------------------|--------------|
| Overall effects (UTI) | 18 | 31.1 (24.1–39.1) | 4.4 0.00 | 0.00 538 | 96.8 1 0.29 |
| Gram-negative | 17 | 69 (23.6–99.5) | 11 0.01 | 0.001 201 | 94 0.32 0.002 |
| Gram-positive | 16 | 31 (12.4–48.4) | 5.7 0.00 | 0.00 65.1 | 90.8 1.2 0.35 |
| Escherichia coli | 18 | 43.4 (38.4–50.1) | 3 0.00 | 0.001 38.1 | 90.1 0.2 0.11 |
| Entrobacter spp. | 8 | 5.4 (2.2–12.9) | 5.8 0.00 | 45.2 0.00 | 84.5 5 0.002 |
| Klebsiella | 14 | 13 (7–19.9) | 5.3 0.00 | 0.00 29 | 78.2 3.6 0.034 |
| Coagulase negative staph | 13 | 10.2 (5.4–18.2) | 8.8 0.001 | 0.00 111 | 81 0.00 0.13 |
| Staphylococcus aureus | 12 | 5.8 (2.7–13.1) | 8.1 0.000 | 0.00 12 | 63 1 0.91 |
| Pseudomonas aeruginosa | 13 | 11.3 (7.9–15.8) | 12.1 0.011 | 0.06 16.5 | 55.2 4 0.03 |
| Streptococcus | 12 | 6 (2–17.7) | 6.2 0.23 | 0.01 44.8 | 92 1.9 0.19 |
| Acinetobacter | 10 | 3 (1.4–5.8) | 13.3 0.00 | 0.08 11.2 | 60.4 1.5 0.16 |
| Enterococcus spp. | 15 | 9 (4–3.9) | 7.1 0.00 | 0.00 88 | 98 1.3 0.002 |

CI=Confidence interval

Table 3: Subgroup meta-analysis of antibiotic resistance pattern for Gram-negative bacteria

| Subgroups | Number of study | Random model | Heterogeneity test | Egger’s test |
|-----------|----------------|--------------|--------------------|--------------|
| Resistance rate (95% CI) (%) | | | | |
| Z | P | P | Q | I | t | P |
| Amikacin | 11 | 39 (33.4–40.5) | 5.5 0.00 | 0.32 5.8 | 92 2.1 0.44 |
| Amoxicillin | 11 | 76 (43.12–91.7) | 2.2 0.01 | 0.03 5.2 | 87 11 0.00 |
| Tobramycin | 10 | 75.1 (34.9–111.2) | 1.8 0.11 | 0.002 23 | 56 0.35 0.43 |
| Kanamycin | 10 | 53 (14.2–61.9) | 13 0.07 | 0.00 8.1 | 72 1.7 0.46 |
| Erythromycin | 10 | 80.1 (46.8–88.2) | 6.1 0.00 | 0.00 12.1 | 76 2.4 0.003 |
| Nitrofurantoin | 12 | 41 (28.5–58.2) | 1.4 0.00 | 0.00 72.1 | 99 0.03 0.5 |
| Cotrimoxazole | 15 | 72 (54.3–91.1) | 3.3 0.013 | 0.00 32.1 | 84 3.7 0.01 |
| Cephalotin | 13 | 58.2 (52.1–69.6) | 4 0.054 | 0.00 8.3 | 27.3 0.34 0.33 |
| Gentamicin | 13 | 48 (41–56.8) | 0.21 0.00 | 0.18 17.3 | 55 0.1 0.26 |
| Ceftriaxon | 10 | 70.1 (55–95.2) | 4.6 0.00 | 0.001 14 | 72 0.1 0.5 |
| Pipracillin | 10 | 47.2 (14.9–77.2) | 1.4 0.9 | 0.00 19 | 82.1 0.00 0.16 |
| Imipenem | 10 | 13 (4.1–30.2) | 1.1 0.00 | 0.00 32 | 84 0.3 0.002 |
| Cefazidime | 10 | 86.3 (47.4–88.6) | 1 0.03 | 0.00 12 | 77 1 0.39 |
| Nalidixic acid | 15 | 45.3 (9.3.71) | 0.7 0.00 | 0.001 38 | 85 0.8 0.21 |
| Cefixime | 10 | 56 (40.3–99) | 1.1 0.05 | 0.001 11.5 | 81 0.3 1 |
| Ciprofloxacin | 16 | 57 (31–72) | 0.32 0.6 | 0.00 43 | 62 4.2 0.11 |
| Chloramphenicol | 13 | 39.7 (30.4–48.8) | 1.7 0.28 | 0.08 17 | 47 0.30 0.7 |
| Polymyxin B | 10 | 43.2 (11.2–81.8) | 0.00 0.13 | 0.00 18 | 82.2 0.00 0.77 |
| Cephalexin | 10 | 89.1 (58.8–102) | 8 0.00 | 0.00 23 | 80.2 2.5 0.002 |
| Carbenicillin | 10 | 87.3 (58.8–99.3) | 8 0.00 | 0.88 0.33 85.8 1.5 0.004 |

CI=Confidence interval
produced by MDR organisms in solid organ recipients, ranging from 6.5% to 56%.[38‑41]

In the present review, subgroup meta‑analysis of antibiotic resistance for Gram‑negative microorganisms showed the most resistance to cephalaxin followed by Carbenicillin and Ceftazidime with the prevalence of 89.1%, 87.3%, and 86.3%, respectively. The least resistance was observed against Imipenem with resistance rate of 13%. Furthermore, the highest resistance of Gram‑positive bacteria reported against amoxicillin and cephalexin with resistance rate of 79% and 74%, respectively. The effective antibiotic for the treatment of Gram‑positive bacteria was reported Polymyxin B (10.6%). Findings of antibiotic resistance for E. coli showed the highest resistance against Cotrimoxazole and Nalidixic acid with resistance rate of 74.1% and 70%, respectively. As well, the best antibiotic for treatment of UTI caused by E. coli was reported Imipenem and Nitrofurantoin with resistance rate of 13.2% and 19%, respectively.

To our knowledge, ampicillin or amoxicillin were used as the standard treatment for UTI, but various studies from around the world show increased resistance to ampicillin and oxacillin.[42,43] In agreement with their results, our results showed high resistance against oxacillin in both Gram‑negative (76%) and Gram‑positive microorganisms (79%), respectively.

Taking into account all these considerations, renal transplant recipients are at high risk for infections caused by MDR strains owing to surgical procedure, long stay in intensive care unit, having underlying diseases, and immunocomponent conditions.[41] Therefore, infection control measures have a positive impact on the prevention of UTI after renal transplantation.

Finally, findings from this systematic review and meta‑analysis showed that the best antibiotics against Gram‑negative bacteria were imipenem. Polymyxin B was an effective antibiotic against Gram‑positive
microorganisms; also, imipenem and nitrofurantoin can be used as the first and second-line treatments of pathogenic E. coli isolated from UTI in kidney transplant recipients.

CONCLUSIONS

Our systematic review and meta-analysis by combining data from previously published studies in Iran showed a noticeable rate of UTI (31.1%) among renal transplant recipients. As well as, a high prevalence of Gram-negative (69%) and Gram-positive (13%) microorganisms was observed, where E. coli (43.4%) and CoNS (10.2%) were the most among Gram-negative and Gram-positive bacteria, respectively. A high resistance rate was seen against almost all antibiotics used for the treatment of UTI caused by both Gram-negative and Gram-positive bacteria, too. Hence, arbitrary and long-term treatment and empirical prescription should be avoided. Therefore, the antibiotics prescription should be based on data achieved from antibiotic susceptibility tests.

Acknowledgments

We would like to thank our colleagues for their help in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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