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ORIGINAL ARTICLE

Fluoroquinolone prophylaxis in preventing BK polyomavirus infection after renal transplant: A systematic review and meta-analysis

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KEYWORDS
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Abstract Previous studies regarding the prevention of BK viremia following renal transplantation with fluoroquinolone have yielded conflicting results. The purpose of this systematic review was to examine the evidence regarding the efficacy of fluoroquinolone in preventing BK polyomavirus infection following renal transplantation. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for research articles published prior to January 2015 using keywords such as "fluoroquinolone," "BK viremia," and "renal transplantation." We extracted all types of study published in English. The primary outcome was BK viremia and viruria at 1 year post-transplantation. Secondary outcomes were BK virus-associated nephropathy (BKVN), graft failure, and fluoroquinolone-resistant infection. We identified eight trials, including a total of 1477 participants with a mean duration of fluoroquinolone prophylaxis of >1 month. At 1 year, fluoroquinolone prophylaxis was not associated with a decreased incidence of BK viremia [risk ratio (RR), 0.84; 95% confidence interval (95% CI), 0.58–1.20). No significant differences in BKVN (RR, 0.88; 95% CI, 0.37–2.11), risk of graft failure due to BKVN (RR, 0.68; 95% CI, 0.29–1.59), or fluoroquinolone-resistant infection (RR, 1.08; 95% CI, 0.64–1.83) were observed between the fluoroquinolone prophylaxis and control groups. The results of this study suggest that fluoroquinolone is ineffective in preventing BK polyomavirus infection following renal transplantation.

Conflicts of interest: All authors declare no conflicts of interests.

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Introduction

Kidney transplantation remains the treatment of choice for patients with end-stage renal disease. Acute rejection rates have been dramatically reduced with the development of potent immunosuppressant regimens; however, other major complications of kidney transplantation, such as BK polyomavirus (BKV) infection, are emerging [1].

Primary BKV infection generally occurs in childhood and persists in the genitourinary tract, remaining quiescent in the majority of immunocompetent hosts. Latent BKV infections in the host or graft reactivate following transplantation and are initially observed in the urine (BK viruria), then in the blood (BK viremia), and ultimately in the allograft [BK virus nephropathy (BKVN)] [2]. Up to 60% and 30% of kidney transplant recipients develop viruria and viremia, respectively [3,4]. A reported 5.5–8% of infected patients progress to BKVN, leading to graft dysfunction and graft loss in more than 50% and 25% of cases, respectively [5,6].

Although antiviral agents, such as cidofovir, leflunomide, fluoroquinolone antibiotics, and intravenous immunoglobulins, have demonstrated efficacy in treating BKV infection, definitive evidence is lacking [2,7–9]. The mainstay of treatment in patients with BK viremia is decreasing the amount of immunosuppression [10,11]. However, immunosuppression reductions must be cautiously conducted because reduced immunosuppression may increase the risk of acute rejection episodes [12,13], and patients often remain viremic [14,15] and long-term outcomes are uncertain [16].

Altogether, there is a substantial clinical need to identify efficacious therapies for preventing BKV infection, particularly in transplant recipients with recurrent episodes of rejection (e.g., highly sensitized patients). In theory, fluoroquinolones represent an appealing therapeutic option for preventing BK viremia. Fluoroquinolones inhibit bacterial DNA replication by targeting the bacterial enzymes, gyrase, and topoisomerase IV. This effect is relevant as the large T antigen of BKV possesses a helicase function that is essential for replication [17,18]. A previous *in vitro* analysis demonstrated that fluoroquinolones can inhibit BKV DNA replication [19].

A retrospective study involving 185 renal transplants reported that patients receiving a 1-month postoperative course of fluoroquinolones had a significantly lower frequency of BK viremia (22.5% vs. 4%, $p = 0.03$) and BKVN (8.75% vs. 4%) compared with untreated patients [20]. However, a recent randomized controlled trial (RCT) demonstrated that administration of levofloxacin for 3 months was not associated with lower BK viremia [hazard ratio (HR), 0.68; 95% confidence interval (CI), 0.26–1.76] or viruria (HR, 0.91; 95% CI, 0.51–1.63) but was instead associated with an increased risk of resistant BKV infection [risk ratio (RR), 1.75; 95% CI, 1.01–2.98] [21]. Several other studies have reported conflicting results [22,23]. Therefore, we conducted this systematic review and meta-analysis to evaluate the efficacy of fluoroquinolones in preventing BKV infection following renal transplantation and provide more convincing evidence to support or reject the use of prophylaxis protocols comprising fluoroquinolones following renal transplantation.

Materials and methods

Types of studies, participants, interventions, and outcomes

In this systematic review and meta-analyses, we included RCTs and observational studies of fluoroquinolone prophylaxis in BKV infection following renal transplantation. We included studies with participants aged >18 years who underwent either deceased donor renal transplantation or living donor renal transplantation. Recipients receiving fluoroquinolone without any other prophylaxis for BK viremia prevention were included.

The primary outcome was the incidence of BK viremia or viruria at 1 year post-transplantation. The secondary outcomes were the incidences of BKVN, BKVN-associated graft failure, and fluoroquinolone-resistant BKV infection.

Search methods for identification of studies

An electronic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials was performed up to January 2015. The search strategy was limited to humans and included the following keywords: "fluoroquinolones," "levofloxacin," "ciprofloxacin," "quinolones," or "BK polyoma viremia" with "renal transplantation," "kidney transplantation," or "renal allograft."

The electronic search was supplemented with a manual search of the reference lists of retrieved articles and other reviews to identify other potential studies. Our search included reference lists of articles, reviews, and editorials irrespective of language, publication status, or blinding. When required, we attempted to contact researchers to obtain data missing from original publications.

Selection of studies

We included comparative studies such as RCTs and observational studies. Two review authors undertook the selection of studies. Review authors independently reviewed the titles and abstracts of all the articles identified by the literature search. Where titles or abstracts did not provide sufficient information, full-text versions were obtained. The same two review authors independently assessed whether studies met the inclusion criteria. In cases where full-text versions did not provide sufficient information, corresponding authors were contacted for further details.

Data extraction and management

A standardized data collection form was designed to extract data regarding study ID (author name and year of publication), study design, type of allograft (living or deceased), sex, mean or median age, immunosuppressive therapy, fluoroquinolone prophylaxis regimen, dose, duration, and length of follow up. Moreover, we extracted data on graft failure, infection, and BKVN. The two review authors independently extracted patient demographics, characteristics, follow-up duration, and primary and

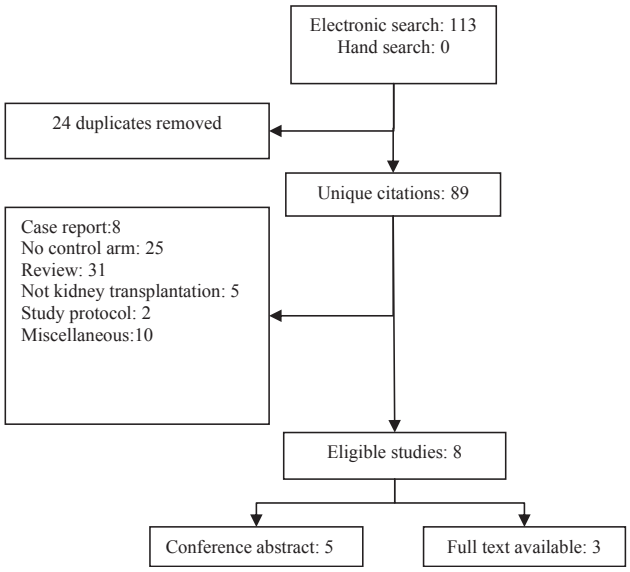

Figure 1. Flowchart of included studies.

secondary outcomes. In case of discrepancy, the opinion of a third reviewer was sought to reach consensus.

Measures of treatment effect

Descriptive statistics were conducted for demographic data. The primary and secondary outcomes (BK viremia, viruria, BKVN, graft failure, and fluoroquinolone-resistant BKV infection) were reported as RRs with 95% confidence intervals. As the majority of included studies were retrospective cohort studies, a random effect model was generated. All p values < 0.05 were considered statistically significant.

Assessment of heterogeneity

The degree of clinical heterogeneity was analyzed on the basis of the dose, duration, type of study, and length of follow up between the two groups. Statistical heterogeneity was analyzed by Cochran Q statistic with the significance level α set at 0.05. The statistic I^2, which is derived from Q, was used to describe the percentage of variation across studies because of heterogeneity rather than chance.

All analyses were performed using Review Manager (RevMan, ver. 5.0; Cochrane Collaboration, Oxford, England).

Results

Description of studies

Overall, eight studies, comprising 1477 renal transplants, were included in the meta-analysis according to the Quality of Reporting of Meta-Analyses guideline criteria (Figure 1). These included two RCTs reporting on a direct comparison of fluoroquinolone versus no treatment or placebo [21,24] and six retrospective cohort studies [20,22,23,25—27]. Unfortunately, full texts were available for only three studies [20,21,25], with the remaining five studies presented as conference abstracts. Although we attempted to contact the corresponding authors, no response was received. One retrospective study utilized both ciprofloxacin and levofloxacin, with the remaining studies using single fluoroquinolone therapy (ciprofloxacin or levofloxacin). Results regarding dose, duration, diagnostic criteria of BK viremia, viruria, and follow-up duration are reported in Table 1.

Assessment of risk of bias

The risk of bias was assessed using the Newcastle—Ottawa scale [28] in all retrospective studies (Table 2). All six retrospective cohort studies were accordingly rated 9/9 [20,22,23,25—27]. Two RCTs investigated the use of fluoroquinolone in preventing BK viremia in renal recipients [21,24]. Only one trial described the process of randomization and allocation concealment and conducted an intention-to-treat analysis and was, therefore, considered to be of "A" quality [24]. The other study could not be assessed because of the limited information provided in the conference abstract and incomplete study [21].

Table 1 Basic information of included studies.

Authors	Year	Study design	Fluoroquinolone	Therapy duration (mo)	BK viremia (copies/mL)	BK viruria (copies/mL)	Follow up (y)
Gabardi et al [20]	2010	Retrospective	Ciprofloxacin (250 mg b.i.d.) Levofloxacin (250 mg q.d.)	1	≥500	—	>1
Wojciechowski et al [25]	2012	Retrospective	Ciprofloxacin (250 mg b.i.d.)	1	≥500	≥1000	1
Jason et al [26]	2013	Retrospective	Ciprofloxacin (250 mg q.d.)	6	—	—	1
Min et al [22]	2013	Retrospective	Ciprofloxacin (250 mg q.d.)	1	>500	—	1
Patel et al [27]	2013	Retrospective	Ciprofloxacin (500 mg q.d.)	3	—	—	1
Eng et al [23]	2014	Retrospective	Ciprofloxacin (250 mg b.i.d.)	1	>1000	—	1
Galen et al [24]	2014	Prospective RCT	Levofloxacin (500 mg daily)	6	—	—	1
Knoll et al [21]	2014	Prospective RCT	Levofloxacin (500 mg daily)	3	>25	≥500	1

b.i.d. = *bis in die* (twice a day); q.d. = *quaque die* (once a day); RCT = randomized controlled trial.

Table 2 Quality assessment of included studies.

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure to implants	Demonstration that outcome of interest was not present at the start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Gabardi et al [20]	A	A	A	B	A	A	A	A
Wojciechowski et al [25]	A	A	A	B	A	A	A	A
Jason et al [26]	A	A	A	B	A	A	A	A
Min et al [22]	A	A	A	B	A	A	A	A
Patel et al [27]	A	A	A	B	A	A	A	A
Eng et al [23]	A	A	A	B	A	A	A	A

Heterogeneity

The included studies were clinically heterogeneous in study design, dose, duration, and diagnostic criteria of BK viremia or viruria. Although statistical heterogeneity ($I^2 > 50\%$) was not noted for all outcomes, high heterogeneity was still considered to be present.

Primary outcome measure: BK viremia

Two RCTs performed a direct comparison of the two strategies for BKV infection prevention and reported no difference in the incidence of BK viremia at 1 year post-transplantation [21,24]. Four cohort studies corroborated the conclusions of this RCT [20–24,26,27]. A higher incidence of BK viremia was even noted in those who received any fluoroquinolone compared with those who received none (14.4% vs. 7.1%, $p = 0.04$), and patients who received fluoroquinolone for 30 days had a higher incidence of BK viremia compared with those who received either fluoroquinolone for less than 30 days or did not receive fluoroquinolone (16.5% vs. 7.6% or 7.1%; $p = 0.02$) [23]. However, two cohort studies reported that patients receiving fluoroquinolone prophylaxis were significantly less likely to develop BK viremia (4% vs. 22.5%, $p = 0.03$ and 10% vs. 25.7%, $p = 0.045$, respectively) [20,22]. When processable data were incorporated, fluoroquinolone prophylaxis was not found to decrease the risk of BK viremia following kidney transplant at 1 year post-transplantation (RR, 0.83; 95% CI, 0.47–1.47; Figure 2). Furthermore, the administration of fluoroquinolone for 1 month (RR, 0.62; 95% CI, 0.14–2.74), 3 months (RR, 0.71; 95% CI, 0.38–1.30), and 6 months (RR, 1.23; 95% CI, 0.45–3.36) had no protective effect on BK viremia at 1 year post-transplantation.

Primary outcome measure: BK viruria

Wojciechowski et al [25] reported BK viruria in 38% and 32% of patients in the control and ciprofloxacin prophylaxis groups, respectively ($p = 0.1738$). Knoll et al [21] reported BK viruria in 22 patients (29.0%) in the levofloxacin group and 26 patients (33.3%) in the placebo group (RR, 0.87; 95% CI, 0.54–1.39). However, these data could not be combined for further analysis.

Secondary outcome measure: BKVN

Galen et al [24] reported one case of biopsy-proven BKVN in the control arm, with no cases in the fluoroquinolone arm. Furthermore, four cohort studies observed no difference in the BKVN occurrence during follow up [20,25–27]. Meta-analysis demonstrated no difference in the incidence of BKVN between the groups (RR, 0.68; 95% CI, 0.29–1.59; Figure 3).

Secondary outcome measure: graft loss due to BKVN

Two studies reported five cases of graft loss due to BKVN in the control arms and no graft loss in the fluoroquinolone

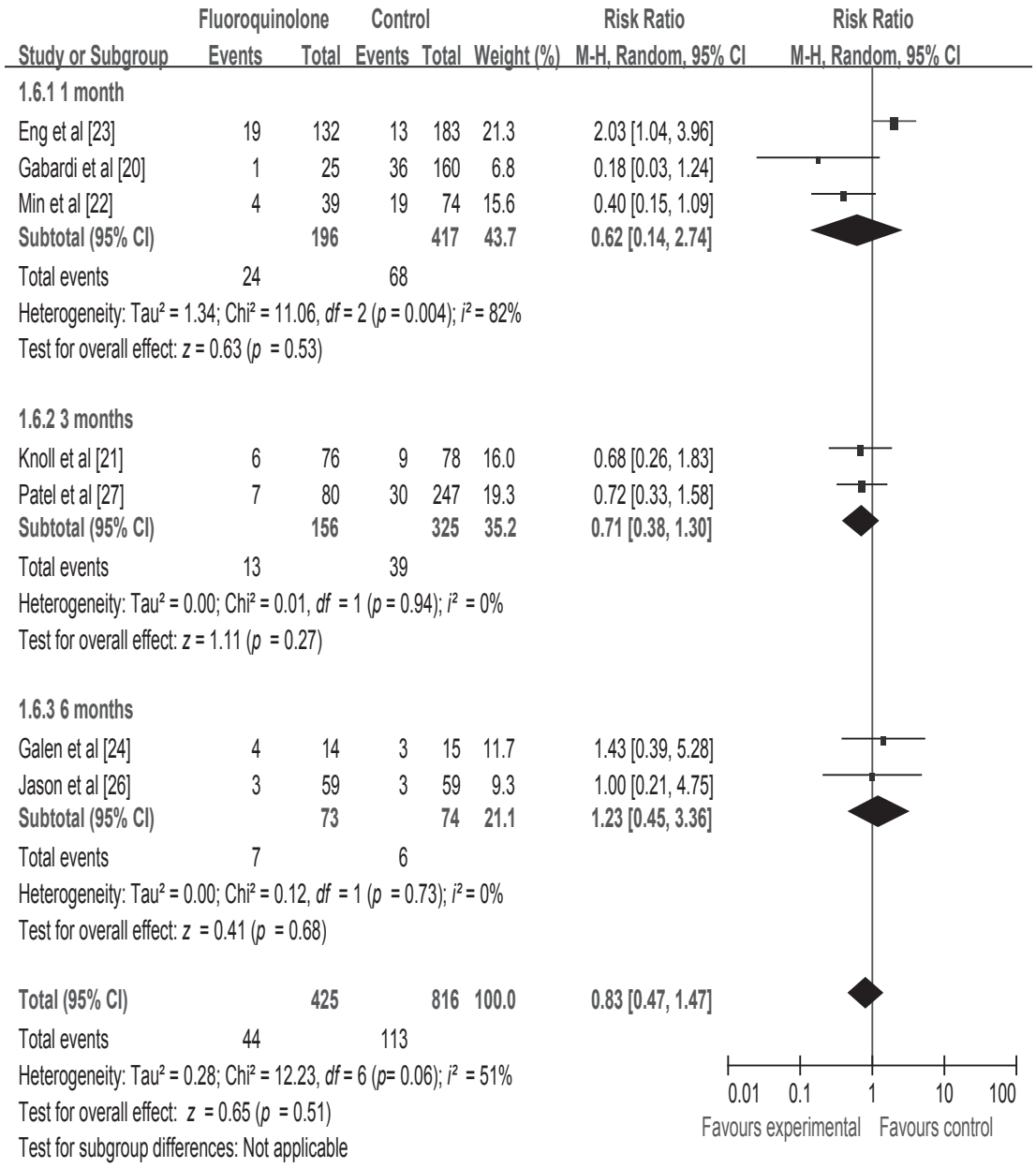

Figure 2. BK viremia at 1 year between the fluoroquinolone prophylaxis arm and the control arm. CI = confidence interval.

arms [20,21]. Pooled analysis demonstrated no difference in the incidence of graft loss between the groups (RR, 0.50; 95% CI, 0.06—4.27; Figure 4).

Secondary outcome measure: fluoroquinolone-resistant infection

Wojciechowski et al [25] reported no difference in the incidence of ciprofloxacin-resistant infections at 12 months post-transplantation between the two groups (4.7% vs. 7.7%, $p = 0.53$), with no difference in the incidence of other fluoroquinolone-resistant infections at 12 months post-transplantation ($p = 0.45$). Similarly, Knoll et al [21] reported a comparable incidence of quinolone-resistant infection in the levofloxacin and placebo groups (46.7% vs. 32.6%; RR, 1.43;95% CI, 0.81—2.50). However, when restricted to isolates usually sensitive to quinolones, the proportion of resistant isolates was much higher in the levofloxacin group than in the placebo group (58.3% vs. 33.3%; RR, 1.75; 95% CI, 1.01—2.98). Pooled analysis demonstrated no difference in the incidence of fluoroquinolone-resistant infection between the groups (RR, 1.08; 95% CI, 0.64—1.83; Figure 5).

Discussion

BKV infection remains a major issue in renal transplantation as it affects up to 30% of kidney recipients and often leads to unfavorable consequences. As there are no effective therapeutic treatments for disease caused by BKV

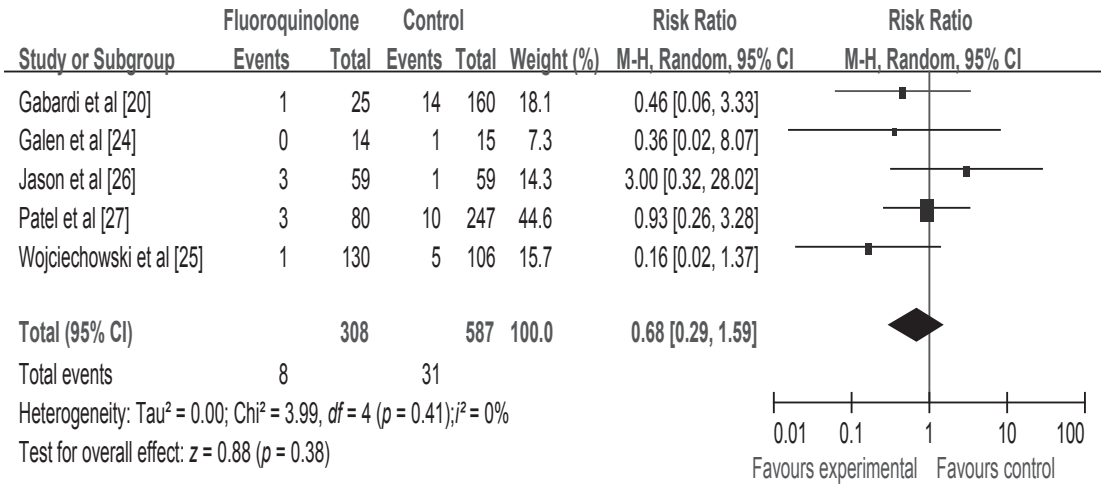

Figure 3. BK virus-associated nephropathy at 1 year between the fluoroquinolone prophylaxis arm and the control arm. CI = confidence interval.

infection, strategies aimed toward the prevention of BK viremia would have considerable clinical benefit in this population. A previous study reported *in vitro* activity of fluoroquinolones against BKV [19], and convincing evidence from hematopoietic stem cell transplant recipients has indicated that ciprofloxacin prophylaxis results in a significant reduction in the incidence of BKV-associated hemorrhagic cystitis [8,29]. However, studies of kidney transplant recipients have yielded inconsistent results. Our pooled analysis revealed that the use of fluoroquinolone prophylaxis does not reduce the incidence of BKV infection. Similarly, rates of BKVN and graft loss due to BKVN were similar between the groups.

Several risk factors for BK viremia, including patient age, male gender, diabetes, white race, induction therapy, and acute rejection, have been identified. Gabardi et al [20] reported favorable results following the use of fluoroquinolone prophylaxis, whereas two other studies did not [21,25]. Induction therapy may have contributed to this discrepancy, with 73%, 53%, and 27.3% of patients receiving antithymocyte globulin in the studies by Gabardi et al [20], Wojciechowski et al [25], and Knoll et al [21], respectively. The rate of acute rejection may also have had an effect, with Gabardi et al [20] and Knoll et al [21] reporting that 18.9% and 7.1% of patients, respectively, developed acute rejection episodes, whereas the rate of acute rejection was not reported by Wojciechowski et al [25]. These results indicate that in patients with higher risk of BKV infection, fluoroquinolone prophylaxis may have a partially protective effect. However, a well-designed and organized RCT is required to confirm this hypothesis.

In general, the most intense period of immunosuppression occurs during the first 3–6 months post-transplantation, with peak BK viremia and the onset of BKVN typically occurring at 3 months [30] and 9–12 months post-transplantation [11], respectively. Of note,

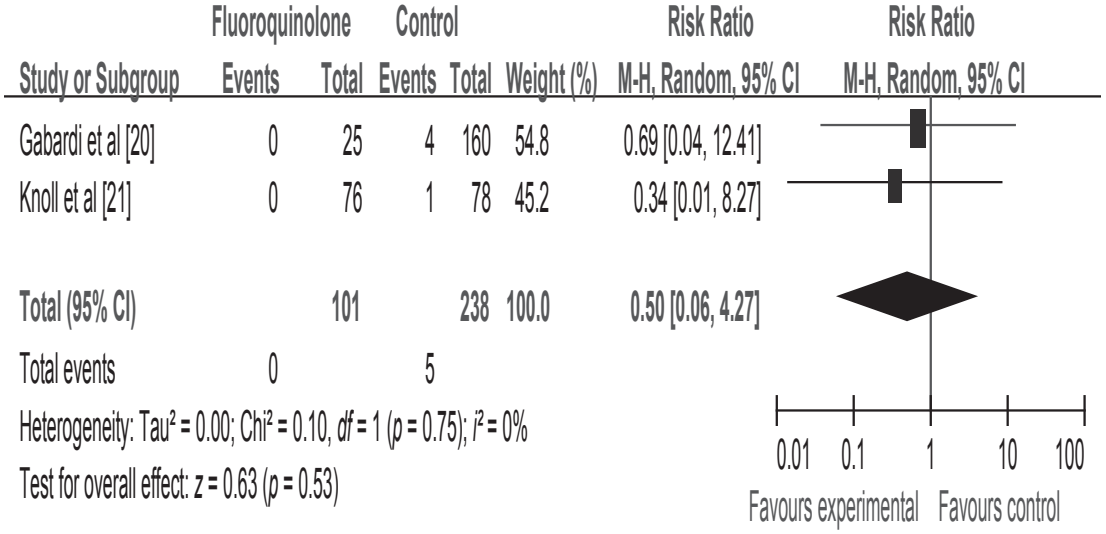

Figure 4. Graft failure due to BK virus-associated nephropathy between the fluoroquinolone prophylaxis arm and the control arm. CI = confidence interval.

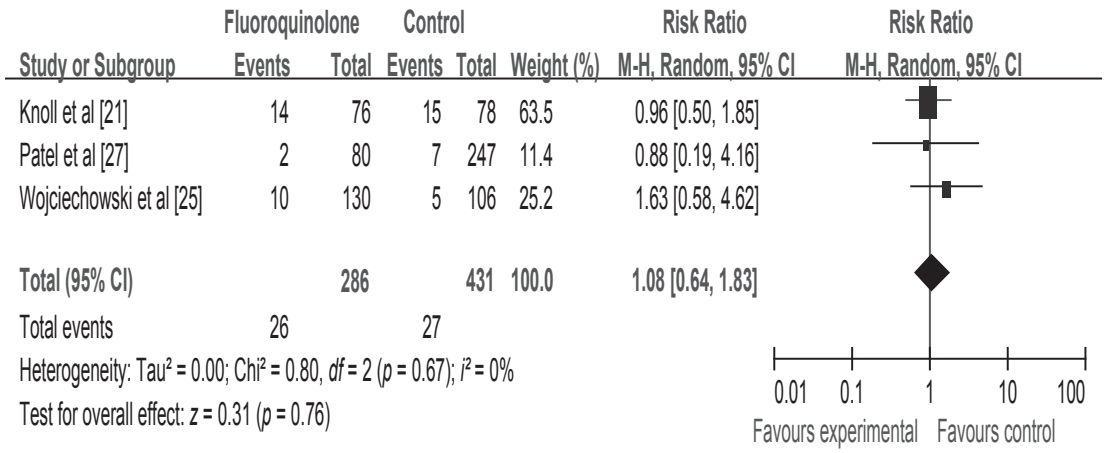

Figure 5. Fluoroquinolone-resistant infection between the fluoroquinolone prophylaxis arm and the control arm. CI = confidence interval.

Wojciechowski et al [25] reported that patients receiving 250 mg ciprofloxacin two times daily for 30 days had a significantly lower risk of developing BK viremia (0.161 vs. 0.065, $p = 0.0378$) and viruria (0.303 vs. 0.146, P = 0.0067) at 3 months post-transplantation; however, this difference disappeared at 12 months post-transplantation for both viremia (0.297 vs. 0.261, $p = 0.6061$) and viruria (0.437 vs. 0.389, $p = 0.5363$). Min et al [22] reported that peak BKV replication appears to be delayed by approximately 1 month in patients receiving ciprofloxacin prophylaxis (5^{th} month vs. 4^{th} month). Longer courses of therapy designed to extend throughout the most intensive period of immunosuppression may be useful in lowering the incidence of BKV infection. However, when studies were stratified according to therapy duration, fluoroquinolone prophylaxis of 3-month and 6-month duration did not reduce the incidence of BKV infection, indicating that longer courses of therapy may not be beneficial.

Fluoroquinolone prophylaxis has been posited as a potential method of decreasing the incidence of urinary tract infections following kidney transplantation. A retrospective study evaluated the incidence of urinary tract infections before and after implementation of a 1-month course of ofloxacin prophylaxis (200 mg every other day). This study demonstrated that ofloxacin was independently associated with a reduction in the incidence of urinary tract infections [odds ratio (OR), 0.31; $p = 0.02$] and acute pyelonephritis (OR, 0.21; $p = 0.045$). The therapeutic effect of ofloxacin prophylaxis was maintained for the 1^{st} year post-transplantation [31]. However, concerns regarding fluoroquinolone therapy remain. First, Knoll et al [21] reported that seven cases of tendinitis occurred, of which six were in the levofloxacin group, thereby demonstrating the potential for concomitant complication following fluoroquinolone administration. Second, long-term use of fluoroquinolone may induce drug-resistant infections as demonstrated by Knoll et al [21] who reported an approximately twofold increase in the rates of resistance among quinolone-sensitive organisms in the levofloxacin group. Patel et al [27] reported several cases of *Clostridium difficile* infections and reduced sensitivity of *Escherichia coli* and *Klebsiella pneumoniae* to many antibiotics. Although this study did not demonstrate a higher incidence of fluoroquinolone-resistant infections, these results have significant implications for clinical practice regarding the management of infections in kidney transplant recipients.

Our study has several limitations. First, the majority of included studies were retrospective cohort studies. Study designs, patient baseline characteristics, therapy dosages and durations, and criteria of BK viremia varied among included studies such that heterogeneity among studies could not be eliminated by generating a random-effect model alone. Furthermore, five conference abstracts provided inadequate information, making it impossible to analyze raw data for individual patients, which is now considered the optimal approach. Finally, the majority of studies did not include BK viruria as a primary measurement, with a proportion of studies not providing this information. However, viremia may be a more relevant clinical outcome because monitoring protocols adjusted to immunosuppression levels are usually based on viremia. During the pathogenesis of BKVN, the detection of viral reactivation in the urine usually precedes the development of both viremia and nephropathy. BK viruria, the first step of BKV infection, may be a higher priority component of screening protocols for evaluating the efficacy of fluoroquinolone prophylaxis.

In conclusion, This meta-analysis demonstrated that the prophylactic use of fluoroquinolones is not effective for preventing BK viremia in kidney transplant recipients and does not reduce the incidence of BKVN or graft loss. These findings do not support the use of fluoroquinolones for the prevention of post-transplantation BKV infection.

Acknowledgments

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