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REVIEW

Infectious complications of endourological treatment of kidney stones: A meta-analysis of randomized clinical trials

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Summary

***Objective:** Endourological treatment is associated with a risk of postoperative febrile urinary tract infections and sepsis. The aim of this study was to review the reported rate of infectious complications in relation to the type and modality of the endourologic procedure.*
***Methods:** This systematic review was conducted in accordance with the PRISMA guidelines. Two electronic databases (PubMed and EMBASE) were searched. Out of 243 articles retrieved we included 49 studies after full-text evaluation.*
***Results:** Random-effects meta-analysis demonstrated that retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL) were associated with not significantly different odds of getting fever (OR = 1.54, 95% CI: 0.99 to 2.39; p = 0.06) or sepsis (OR = 1.52, 95% CI: 0.37 to 6.20, p = 0.56). The odds of getting fever were not significantly different for mini PCNL compared to standard PCNL (OR = 1.11, 95% CI: 0.85 to 1.44; p = 0.45) and for tubeless PCNL compared to standard PCNL (OR = 1.34 95% CI: 0.61 to 2.91, p = 0.47). However, the odds for fever after PCNL with suctioning sheath were lower than the corresponding odds for standard PCNL (OR = 0.37, 95% CI: 0.20 to 0.70, p = 0.002). The odds of getting fever after PCNL with perioperative prophylaxis were not different from the corresponding odds after PCNL with perioperative prophylaxis plus a short oral antibiotic course (before or after the procedure) (OR = 1.31, 95% CI: 0.71 to 2.39, p = 0.38).*
***Conclusions:** The type of endourological procedure does not appear to be decisive in the onset of infectious complications, although the prevention of high intrarenal pressure during the procedure could be crucial in defining the risk of infectious complications.*

KEY WORDS: *Kidney calculi; Percutaneous nephrolithotomy; Retrograde intrarenal surgery; Ureteroscopy; Lithotripsy; Systemic inflammatory response syndrome; Sepsis; Fever; Urinary tract infection.*

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INTRODUCTION

Percutaneous and retrograde endourological procedures are widely used for the removal of renal stones. These treatments ensure high stone free rates and are associated with a relatively low morbidity. However, infectious complications are not uncommon in both.
After *retrograde intrarenal surgery* (RIRS), the rate of febrile urinary tract infections can range between 7.6 and 13.4% (1). Risk factors include preoperative pyuria, stone size, struvite stone composition, operating time, irrigation flow rate and volume, size of ureteral access sheath, presence of residual fragments, history of urinary tract infections, and comorbidities (2-5). The incidence of fever after percutaneous nephrolithotomy (PCNL) was reported to range between 10.4% and to 18.9%, with urosepsis in 0.9% to 4.7% of cases. Longer operating time, higher number of punctures, tract size, staghorn stone, severe preoperative hydronephrosis, preoperative stenting, history of recurrent urinary tract infection, renal failure, and type 2 diabetes were found to be risk factors (6-9).
The aim of this systematic review was to assess the reported rate of infectious complications in relation to the type of endourologic procedure, the methods used in the procedure and the antibiotic prophylaxis applied.

MATERIALS AND METHODS

This review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (10) after being registered on the PROSPERO platform (CRD42021283094). Two electronic databases (*PubMed and EMBASE*) were searched for articles published up to September 30th, 2021.

Search was performed including MeSH terms (*percutaneous nephrolithotomy, ureteroscopy, lithotripsy, kidney calculi, Systemic Inflammatory Response Syndrome, Sepsis, Fever, Urinary Tract Infections*) and was implemented by free-text terms (micro-percutaneous nephrolithotomy, PCNL, mini-PCNL, retrograde intrarenal surgery, flexible ureteroscopy, RIRS, FURS, ECIRS).

The following search terms were used: (percutaneous nephrolithotomy OR ureteroscopy OR lithotripsy OR micro-percutaneous nephrolithotomy OR PCNL OR mini-PCNL OR retrograde intrarenal surgery OR flexible ureteroscopy OR RIRS OR FURS OR ECIRS) AND kidney calculi AND (systemic inflammatory response syndrome OR sepsis OR fever OR urinary tract infections).

Relevant data were also hand searched by browsing various sources (*e.g., reference lists from reviews and study reports, congress abstracts, www.clinicaltrials.gov, www.clinicaltrialsregister.eu, and others*).

During the initial screening of the retrieved records we considered *randomized controlled trials* (RCTs), with an open-label or single/double blinded design including participants without restriction of age or gender or ethnicity, treated for renal stones with percutaneous endoscopic procedures (including standard PCNL, mini-PCNL, ultramini- or micro-PCNL) and retrograde endoscopic procedures (flexible ureteroscopy or RIRS). Article reporting comparisons between *Endoscopic Combined Intrarenal Surgery* (ECIRS) and single endoscopic procedures (both percutaneous and retrograde) were also initially examined.

In this systematic review we included articles reporting the comparison of infectious complication rates in:

1) PCNL *vs* RIRS, 2) standard PCNL *vs* miniaturized PCNL, 3) tubeless *vs* non tubeless PCNL, 4) PCNL or RIRS with/without use of suctioning sheath, and 5) PCNL/RIRS under different modalities of antibiotic prophylaxis.

The following outcomes were considered: fever > 38°C or sepsis according to *Systemic Inflammatory Response Syndrome* (SIRS) or *Sequential Organ Failure Assessment* (SOFA) scores.

The *Systemic Inflammatory Response Syndrome* (SIRS) score had been used since 1991. It is calculated based on the presence of the following criteria: temperature > 38°C or < 36°C, heart rate > 90/minute, respiratory rate > 20/minute, WBC > 12,000 or < 4,000 (11). The SOFA score was introduced by the Sepsis-3 Task Force in 2016. The quick SOFA (qSOFA) score is a simpler scoring system based on the presence of a respiratory rate ≥ 22 /min, a systolic blood pressure ≤ 100 mmHg, and altered mental status (12).

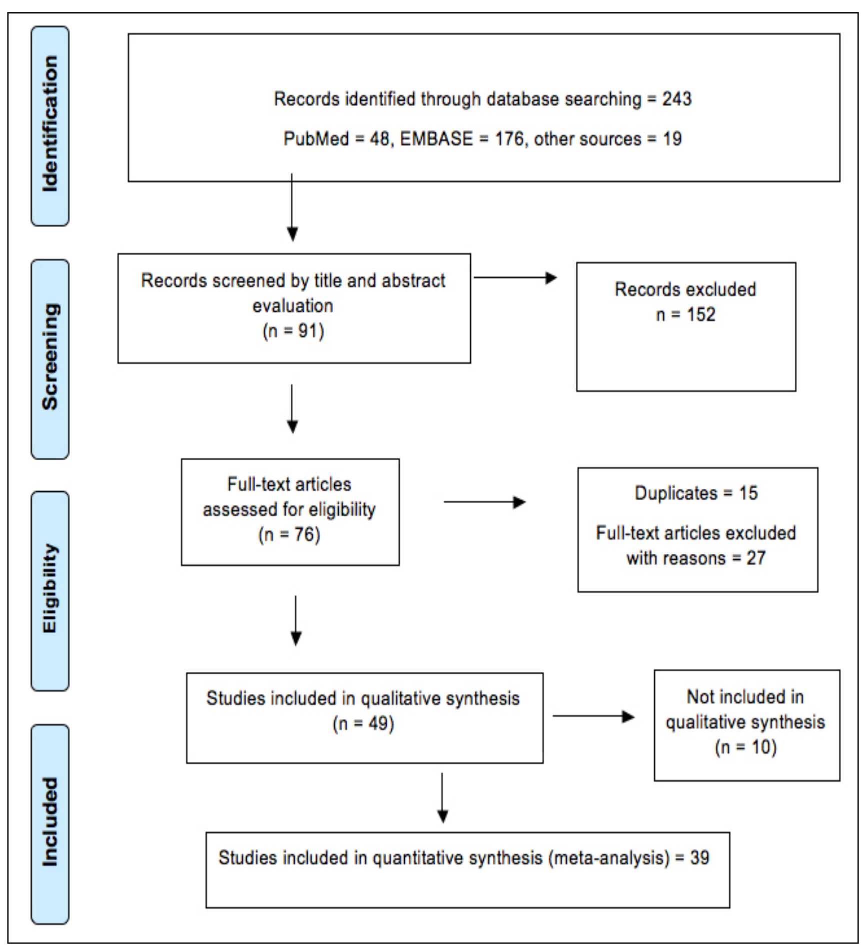
Title and abstract screening to exclude documents that did not meet the inclusion criteria were performed independently by two authors. Controversies were resolved by a third researcher. Duplicate references were excluded and full texts of the screened articles were analyzed to confirm their inclusion in the review. A PRISMA flow diagram was drawn to illustrate the results of the study selection process (Figure 1).

Data extraction was conducted by two authors using a standardized form. The following information was obtained from each study: author(s), publication year, study design, population, intervention, rate of infectious complications (fever, SIRS, sepsis) (see *Supplementary Materials - PICO tables*). The risk of bias of randomized controlled trials was assessed using the *Risk of Bias* (RoB) 2 assessment tool as prescribed by the Cochrane Handbook (13). The quality of each study was independently assessed by two reviewers (DH and HAG-P) against pre-defined criteria in relation to the randomization process (D1), deviations from the intended interventions (D1), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported result (D5). Disagreements were resolved by discussion.

The presence of risk of bias was not used as a criterion to exclude studies from this review or from meta-analysis (see *Supplementary Materials - RoB*).

Statistical analysis was performed using the RevMan5 software. Dichotomous data (presence/absence of infectious complications) and number of per-protocol or intent-to-

Figure 1.
Flow chart.



treat patients were extracted to calculate *odds ratios* (OR), *confidence intervals* (CI) to odds-ratios, and Z statistics (Random-effects model, Mantel-Haenszel method). Forest plots were drawn in the presence of more than three studies.
Heterogeneity was assessed by I^2 statistics, reported with 95% CIs, and interpreted as of lesser importance (≤ 40%), moderate (30%-60%), substantial (50%-90%) or considerable (≥ 75%), according to Cochrane criteria.
Summary of Findings tables for comparisons outlined in Forest plots were prepared. The quality of evidence was rated according to GRADE criteria (see *Supplementary Materials - Summary of findings*).
Funnel plots were drawn to assess report bias. Publication bias was assessed by visually inspecting the funnel plots (see *Supplementary Materials - Publication bias*). If a potential reporting bias was suspected, the Egger's regression and Begg's correlation tests were applied to assess the significance of funnel plot asymmetry and to confirm the perceived publication bias. Asymmetry tests were performed using the MetaEssentials 1 software (*Rotterdam School of Management, Erasmus University, The Netherlands*).
The 'trim and fill' missing study imputation approach was applied to asymmetric funnel plots and adjusted overall effect sizes were calculated.

Results

From our primary search we retrieved 48 articles from PubMed, 176 from EMBASE and 19 from other sources. Title and abstract screening allowed us to select 91 articles (21 from PubMed, 62 from EMBASE and 8 from other sources), that were reduced to 76 after removal of 15 duplicates. After full-text evaluation, 27 articles were excluded (2 articles reporting about pediatric populations, 4 articles reporting data of patients which were part of studies already included in this review, 13 articles for insufficient reporting, 6 articles dealing with a topic not included in the analysis, and 2 articles reporting the results of non-randomized studies) (Table 1).
Finally, 49 studies were included in qualitative analysis (14-62), of which 39 were suitable for quantitative analysis.

RIRS vs PCNL
We retrieved 20 articles (6 from Pubmed, 11 from EMBASE, 3 from other sources). After removal of 4 duplicates and one article involving a pediatric population, 15 studies were included in the analysis (14-28). Out of 15 studies, 11 evaluated post-operative fever (14-16, 18, 20-23, 25, 27, 28), 2 sepsis (17, 24), and 2 both post-operative fever and sepsis (19, 26).

Standard PCNL vs mini/ultra mini/supermini/micro PCNL
We retrieved 17 articles (1 from PubMed, 14 from EMBASE, 2 from other sources). After removal of one duplicate, 16 full-text articles were evaluated.
Two articles were excluded because they reported data from the same study, and 5 more for insufficient data reporting. Finally, 8 articles were included in the analysis (29-36) and one article reporting a comparison of mini-PCNL with ultramini-PCNL (37) was considered for qualitative analysis.

Standard PCNL vs tubeless PCNL
We retrieved 21 articles (4 from PubMed, 17 from EMBASE). After removal of 3 duplicates, 18 full-text articles were evaluated.
Nine articles were excluded (one involving a pediatric population, 5 for insufficient reporting, 2 comparing tubeless PCNL within different size tracts, and 1 not randomized).
Out of the 9 articles included in the analysis, 6 articles compared tubeless with standard PCNL (38-43), 2 articles compared tubeless PCNL with tubeless PCNL with use of sealant (44, 45), and one study tubeless PCNL with and without infiltration of the tract with bupivacaine (46).

Standard PCNL/RIRS vs vacuum-assisted
We retrieved 11 articles (2 from PubMed 9 from EMBASE). After exclusion of 2 duplicates, 9 articles were included for full text evaluation: 2 were excluded because they reported data of patients which were part of studies already included in this review, 2 because they reported series of ureteral stones, and 1 for its retrospective design.
Out of the remaining 4 articles, 3 reported about the use of a vacuum-assisted access sheath for PCNL (47-49), and one the use of ureteral access sheaths for RIRS (50).

Perioperative prophylaxis
We retrieved 22 articles (8 from PubMed, 11 from EMBASE and 3 from other sources).
After removal of 5 duplicates, 17 articles were evaluated by full-text reading. Two articles were excluded because they were off-topic (comparison with open surgery, ureteral stones) and 3 because of incomplete reporting.

Table 1.
Results of the selection process divided by topic and procedure.

	PubMed	EMBASE	Other sources	Total	Duplicates	Evaluated	Excluded	Included
RIRS *vs* PCNL	6	11	3	20	4	16	1	15
sPCNL *vs* mini	1	14	2	17	1	16	7	9
Tubeless	4	17	0	21	3	18	9	9
Sheath	2	9	0	11	2	9	5	4
Prophylaxis	8	11	3	22	5	17	5	12
Total	21	62	8	91	15	76	27	49

Reasons for exclusion	Pediatric population	Insufficient data reporting	Reporting same series	Reporting topics not included in the analysis	Not randomized
RIRS vs PCNL	1				
sPCNL *vs* mini		5	2		
Tubeless	1	5		2	1
Sheath			2	2	1
Prophylaxis		3		2	
Total	2	13	4	6	2

Out of the 12 remaining articles (51-62), one study compared perioperative antibiotic prophylaxis with a short course of antibiotics in patients at high risk for infectious complications (51), 5 studies (52-56) compared the effect of perioperative antibiotic prophylaxis with a single dose (or with two doses 24-48 hours apart) with a more complex strategy associating perioperative prophylaxis with a short course of antibiotic in the preoperative or postoperative period, 2 studies compared the results of perioperative prophylaxis with different antibiotics (57, 58), and 2 studies compared both perioperative prophylaxis with different antibiotics and different strategies of antibiotic prophylaxis (59, 60).
Finally, two randomized placebo-controlled studies evaluated the outcome of antibiotic prophylaxis in patients who underwent PCNL or RIRS (61, 62).

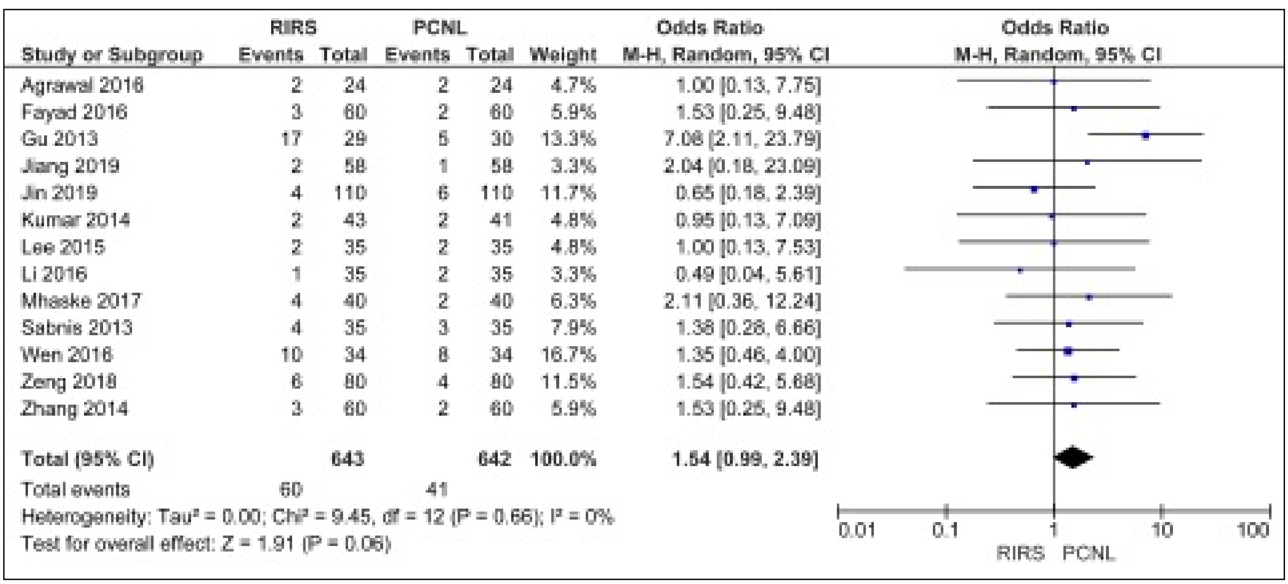
was considered low in 44 studies and unclear in 5 and risk of bias in selection of the reported results was judged low in 38 studies, unclear in 10 and high in one.
In total risk of bias was considered low in 10, unclear in 28 and high in 11.

Meta-analysis

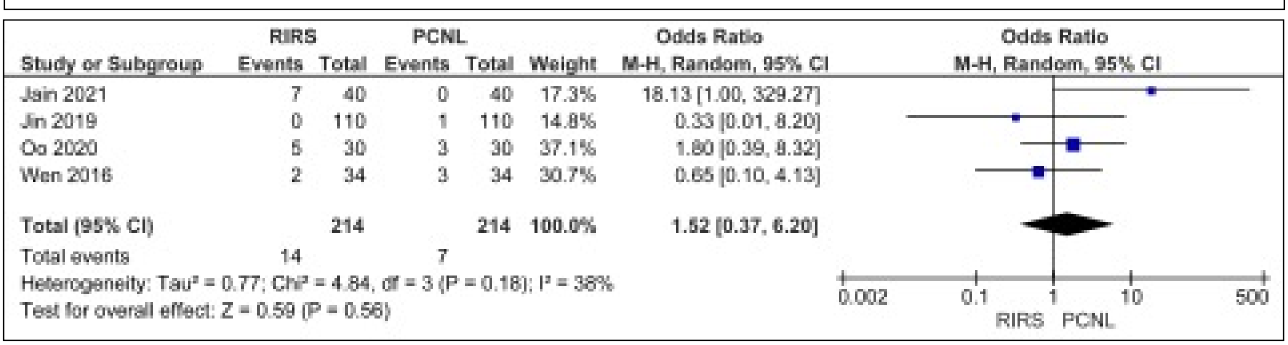
RIRS vs PCNL
Random-effects meta-analysis revealed that *retrograde intrarenal surgery* (RIRS) and *percutaneous nephrolithotomy* (PCNL) were not associated with significantly different odds of getting fever (OR = 1.54, 95% CI: 0.99 to 2.39; 13 trials, 1285 participants, Z = 1.91, P = 0.06, I^2 = 0%) or sepsis (OR = 1.52, 95% CI: 0.37 to 6.20; 4 trials, 428 participants, Z = 0.59, P = 0.56, I^2=38%) (Figures 2a, 2b).

Figure 2a, b.
Odds of getting fever (plot a) or sepsis (plot b) after RIRS or PCNL
(plot labels: on the right: favors PCNL; on the left: favors RIRS)
[explanation: the Gu trial favors PCNL because RIRS shows more febrile events: thus the Gu point is on the right: less febrile events with PCNL]

a.



b.



Risk of bias
Of the 49 studies, 25 described methods of randomization with low risk of bias, 17 with unclear risk and 7 with high risk. We judged the risk of deviations from the intended intervention as low in 24 studies, unclear in 22 and high in 3.
Missing outcome data was judged low in 35 studies and unclear in 14. Risk of bias in measurement of outcome

Mini vs standard PCNL
The odds of getting fever were not significantly different when mini-PCNL was compared to standard-PCNL (OR = 1.11, 95% CI: 0.85 to 1.44; 8 trials, 2774 participants, Z = 0.76, P = 0.45, I^2 = 0%) (Figure 3).
A study of *Sabnis et al.*, not included in the meta-analysis compared mini-PCNL (12 F) with ultramini-PCNL (7.5 F) for treating stone of a size < 1.5 cm, demonstrat-

Figure 3.
Odds of getting fever after miniaturized PCNL (mini-PCNL) compared to standard PCNL (S-PCNL).
(plot labels: on the right: favors standard PCNL; on the left: favors mini-PCNL)

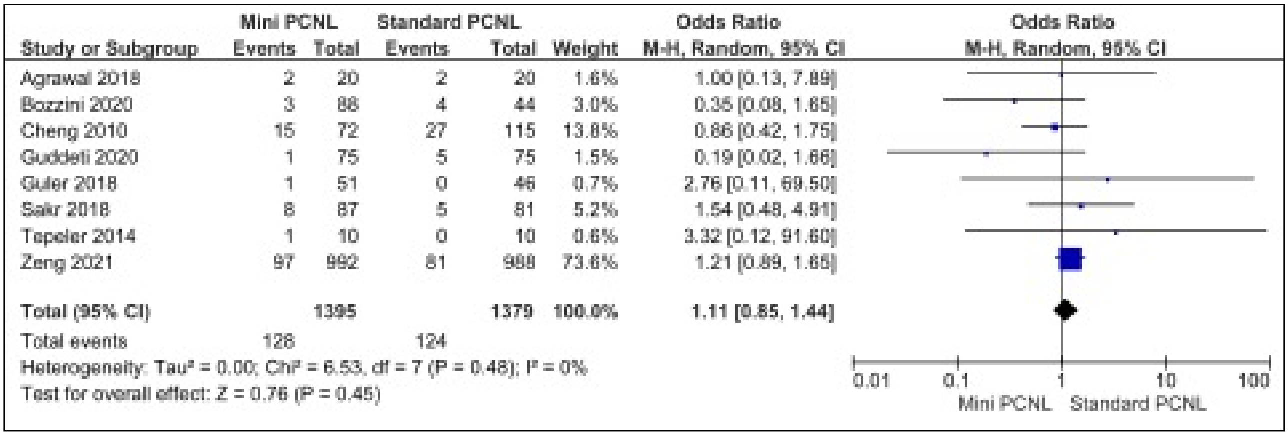
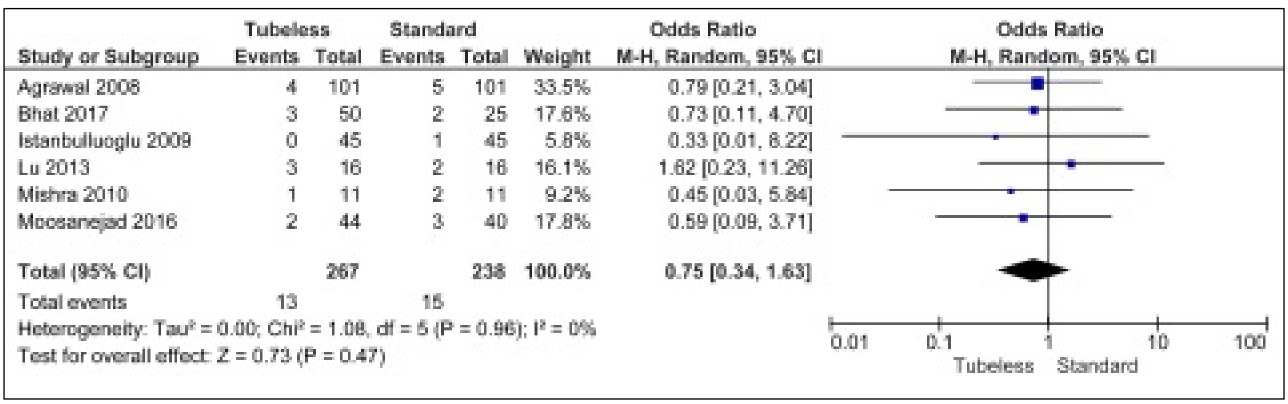


Figure 4.
Odds of getting fever after tubeless PCNL (TL-PCNL) compared with standard PCNL (S-PCNL)
(plot labels: on the right: favors S-PCNL; on the left: favors TL-PCNL)



ing comparable rates of postoperative sepsis (0/30 *vs* 1/30) (37).

Tubeless PCNL vs standard PCNL

The odds for fever were not significantly different when tubeless-PCNL was compared to standard-PCNL (OR = 0.75 95% CI: 0.34 to 1.63; 6 trials, 505 participants, Z = 0.73, P = 0.47, I^2 = 0%) (Figure 4).

Two studies, not included in the pooled analysis, compared the rate of infectious complications after tubeless PCNL vs. tubeless PCNL with use of sealant.

Shah et al (44) showed similar rates of fever after tubeless PCNL with or without sealant (1/32 *vs* 2/31). Similar results were obtained by *Titaram et al.* (45) with similar rates of fever (19/41 *vs* 15/41, P = 0.20), lower rate of SIRS with use of sealant (but one case of sepsis versus none).

Another study compared the results of tubeless PCNL with or without infiltration with bupivacaine (rate of fever 7/46 *vs* 6/23, P = 0.49)(46).

PCNL/RIRS with suctioning sheath vs standard PCNL

The odds of getting fever for PCNL with suctioning sheath were significantly lower than the odds calculated for standard PCNL using a normal Amplatz sheath (OR = 0.37, 95% CI: 0.20 to 0.70; 3 trials, 351 participants, Z = 3.10, P = 0.002, I^2 = 0%) (Figure 5).

A single randomized trial not included in the meta-analysis, evaluated the risk of getting fever after RIRS with the use of suctioning sheath compared to the standard procedure. *Eisner et al.* (50) presented the results of a randomized trial including 20 patients: no infectious complication was observed in the group treated with aspiration through the access sheath, while one patient in the control group had a urinary tract infection.

Antibiotic prophylaxis (comparison with placebo)

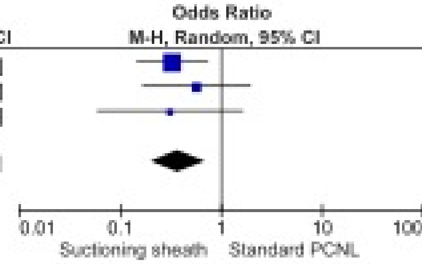
Two studies were retrieved and not pooled, as they compared different antibacterial agents with placebo (61, 62).

A multicentre randomized trial (61) compared the result of preoperative prophylaxis in PCNL with a single dose of cefotaxime (1 gr) with placebo. The rate of postoperative bacteriuria was lower in patients treated with cefotaxime although the difference was not statistically significant, likely due to the low number of patients treated with PCNL included in the study. Similarly, clinical data about the rate of postoperative fever and urinary tract infection were not available because the data relative to PCNL were aggregated with those of ureterorenoscopy.

A study presented the results of preoperative prophylaxis

Figure 5.
Odds of getting fever after PCNL with suctioning sheath (PCNL + SS) compared with standard PCNL (S-PCNL) (plot labels: on the right: favors S-PCNL; on the left: favors PCNL + SS).

	Suctioning sheath		Standard PCNL			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Huang 2016	10	91	25	91	60.0%	0.33 [0.15, 0.73]
Lai 2020	5	38	8	38	25.9%	0.57 [0.17, 1.93]
Zhong 2021	2	46	6	47	14.1%	0.31 [0.06, 1.63]
Total (95% CI)		**175**		**176**	**100.0%**	**0.37 [0.20, 0.70]**
Total events	17		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						



of RIRS with ciprofloxacin compared with placebo (62). The rate of RIRS after placebo (9.9%) was not significantly different from the rate assessed following treatment with one (4.9%) or two doses of ciprofloxacin (4.2%). However, a subgroup analysis demonstrated a significantly higher risk of getting SIRS in patients who received placebo for treatment of stones > 200 mm^2 compared to patients who received ciprofloxacin (18% vs single dose 4.3%, P = 0.036; vs two doses 5.5%, P = 0.044).

Antibiotic prophylaxis (comparison of antibiotics)

Four studies were retrieved and not pooled, as they compared different antibacterial agents administered according to different treatment protocols (57-60).

Song et al. (57) administered to patients who underwent PCNL a three-day course of oral fosfomycin (3 g/day) *vs.* intravenous cefuroxime (3 g/day). Fosfomycin proved to be more effective than cefuroxime, exerting a high antibacterial effect on pathogens localized in the stone, thus reducing the probability of infection. Postoperative fever was observed in 7/31 patients in the experimental group compared to 9/30 in the control group (p > 0.05) but SOFA score was > 2 in 3/31 versus 10/30 (p < 0.05).

Seyrek et al. (58) did not observe significant differences in the risk of getting SIRS after PCNL in patients treated with sulbactam-ampicillin versus cefuroxime (13.7 *vs* 17.7%, P = 0.44), though one patient in the sulbactam-ampicillin died of septic shock. Similarly, *Taken et al.* (59) observed no difference in the rate of SIRS following PCNL in patients treated with ceftriaxone (23.3%) or cefazoline (12.5%) (P = 0.264). Finally, *Demirtas et al.* (60) found no difference in the rate of SIRS after PCNL between ciprofloxacin (15.5%) and ceftriaxone (8.8% P = 0.52).

Perioperative vs perioperative plus additional short antibiotic prophylaxis

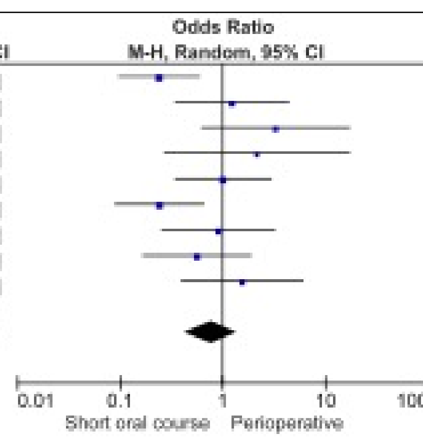
Seven studies reported the results of the comparison of perioperative antibiotic prophylaxis versus perioperative prophylaxis associated with prolonged oral administration of antibiotics in patients who underwent PCNL for stones. Patients were deemed to be at low risk for infectious complications (negative preoperative urine culture, absence of hydronephrosis). Two studies (*Seyrek* 2012 and *Demirtas* 2012) (58, 60) included data about the use of two different antibiotics, data were pooled separately.

The odds for fever after PCNL with perioperative prophylaxis were not different than after PCNL with perioperative prophylaxis plus a short oral antibiotic course (before or after the procedure) (OR = 0.76, 95% CI: 0.42 to 1.40; 9 trials, 720 participants, Z = 0.87, P = 0.38, I^2 = 53%) (Figure 6).

A study (not included in the meta-analysis) (51) compared the outcome of 2 days *vs.* 7 days of preoperative antibiotics in patients at moderate-to-high risk for sepsis undergoing percutaneous nephrolithotomy. The sepsis rates were not different between treatment arms on uni-

Figure 6.
Odds of getting fever after PCNL with perioperative prophylaxis (PP) compared with PCNL with perioperative prophylaxis plus a short oral antibiotic course (PP + SOC)(plot labels: on the right: favors perioperative; on the left: favors PP + SOC).

	Short oral course		Perioperative			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bag 2011	9	48	26	53	14.7%	0.24 [0.10, 0.59]
Chew 2018	6	43	5	43	11.1%	1.23 [0.35, 4.39]
Demirtas 2012	4	15	3	30	8.3%	3.27 [0.63, 17.09]
Demirtas 2012b	2	15	2	30	6.1%	2.15 [0.27, 17.02]
Dogan 2002	8	38	9	43	12.9%	1.01 [0.35, 2.94]
Mariappan 2006	7	52	18	46	13.7%	0.24 [0.09, 0.65]
Seyrek 2012	4	31	9	64	11.2%	0.91 [0.26, 3.21]
Seyrek 2012b	4	32	13	64	11.6%	0.56 [0.17, 1.88]
Tuzel 2013	6	37	4	36	10.4%	1.55 [0.40, 6.02]
Total (95% CI)		**311**		**409**	**100.0%**	**0.76 [0.42, 1.40]**
Total events	50		89			
Heterogeneity: Tau² = 0.44; Chi² = 16.98, df = 8 (P = 0.03); I² = 53%						
Test for overall effect: Z = 0.87 (P = 0.38)						



variate analysis. However multivariate analysis showed that the risk of sepsis was increased (OR = 3.1, 95% 1.1-8.9, P = 0.031) in patients who were treated for 2 days compared to patients who were treated for 7 days.

Publication bias analysis

Figure 1 a-f (see *Supplementary Materials - Publication bias analysis*) shows the funnel plots relative to the 6 pooled analyses performed in this systematic review.

Table 1 (*Supplementary Materials - Publication bias analysis*) shows the significance values of the Begg's and Egger's asymmetry tests.

The only pooled analysis showing significant asymmetry (Egger's P = 0.011, Begg's P = 0.004) was the one comparing perioperative prophylaxis vs. perioperative prophylaxis plus an additional short antibiotic prophylaxis. The "Trim-and-fill" strategy imputed two missing studies to the asymmetric funnel plot. The adjusted odds ratio of the funnel plot including the imputed missing studies was 0.62 (95% CI: 0.31 to 1.28). Thus, despite the addition of two imputed studies, the odds ratio for this comparison remains not significant.

Summary of findings

Tables 1 a-e (*Supplementary Materials - Summary of findings*) present the summary of the findings of the meta-analyses, also including an evaluation of the quality of the evidence, performed according to GRADE criteria.

The quality of the evidence was rated as low for the comparisons (i) PCNL with suctioning sheath *vs.* standard PCNL, and (ii) PCNL with simple perioperative antibiotic prophylaxis (PAP) plus a short oral antibiotic course *vs.* PCNL with simple PAP. The reasons for downgrading the former were risk of bias (one point) and imprecision due to the low number of participants (one point). The reasons for downgrading the latter were risk of bias (one point) and publication bias (one point). The quality of the remaining evidence was rated as moderate, mainly due to the presence of risk of bias (one point).

Discussion

Endourological treatment of kidney stones represents a considerable improvement in the management of nephrolithiasis, thanks to the reduction of morbidity and the minimal surgical impact on the urinary tract.

The complications associated with this form of treatment are relatively infrequent, though serious bleeding and infectious complications can be observed.

PCNL and RIRS are treatment modalities that have specific indications. However, the choice of a specific procedure is based on the experience of the operating surgeon and sometimes on the patient's preferences. In fact, kidney stones smaller than 20 mm can alternatively be treated with percutaneous or retrograde intracorporeal lithotripsy (63). In this case, the risk of complications should be taken into consideration when choosing between the two forms of treatment.

Retrograde and percutaneous renal stone treatment can affect the risk of infectious complications in different ways.

Flexible ureteroscopy can increase intrarenal pressure in relation (i) to type and rate of irrigation, or (ii) to the use and size of ureteral sheaths promoting the anterograde outflow of irrigation fluid. The increase in pressure within the urinary tract can cause an intratubular reflux of urine, with increased risk of infectious complications.

Percutaneous treatment does not generally involve a major increase of fluid pressure in the urinary tract, but it can cause greater local trauma and extravasation of irrigating fluid.

Previous meta-analyses have compared the results of percutaneous nephrolithotomy with the outcomes of retrograde intrarenal surgery for the treatment of kidney stones. However, the risk for infectious complications was not included in such analyses.

Zheng et al. (64) found no difference in the rate of postoperative fever (RR = 0.95, P = 0.85) between RIRS and PCNL. More recently, *Chen et al.* (65) reviewed 11 studies showing that the rate of postoperative fever or infection was not significantly different in the patients treated with PCNL compared to those treated with RIRS (RR = 1.26, P = 0.29).

Our study included only 5 of the 11 studies considered by *Chen et al.* because we limited our search to randomized controlled studies. Furthermore, we found and included in the analysis 10 additional randomized studies. However, we were not able to demonstrate a significant superiority of one endourological procedure over the other with regards to the risk of postoperative fever or sepsis. However, we observed a trend for a higher risk of fever after RIRS (OR = 1.54, 95% CI: 0.99 to 2.39).

It should be highlighted that most comparative studies had as a primary endpoint the evaluation of stone-free status after treatment rather than the occurrence of infectious complications.

Based on the results of our meta-analyses, the choice of the procedure would not seem to be a relevant factor for infectious complications after treatment.

However, the risk of infectious complications could depend on how PCNL and RIRS are performed. In our analysis, we were able to examine the impact of certain treatment procedures on the risk of infection. For PCNL, we considered the effect of the diameter of the scope and of the indwelling time of the nephrostomy after the procedure. For both PCNL and RIRS we considered the impact of the use of a suction system for the irrigating fluid and the use of different methods of antibiotic prophylaxis.

Unfortunately, it was not possible to evaluate other characteristics of the interventions - such as prolonged operating time (> 1 hour), type and rate of irrigation, use of sheath and pre-operative stenting (for RIRS) - due to the lack of information within the reports of the studies included in the analysis.

The comparison of standard PCNL with miniaturized PCNL including mini-PCNL, ultramini-PCNL, and micro-PCNL showed no significant difference in the odds for infectious complications despite a higher potential intra-renal pressure with the latter two.

The benefits of reduced trauma due to the smaller diameter of the scope could be counteracted by lesser control of intrarenal pressure associated with miniaturized procedures. In fact, a review on the evidence related to intrarenal pressures generated during percutaneous procedures found that standard PCNL is associated with the lowest pressure values. On the contrary, pressure values during mini-PCNL can be decreased by using the vacuum-cleaner effect, but pressure might still be uncontrolled during micro- and ultra-mini PCNL procedures (66).

We also found that avoidance of nephrostomy drainage in the postoperative period is not associated with an increased risk of infection after a standard procedure.

The use of suction systems through the access sheath seems to reduce the risk of infection, since in addition to the improved clearance of fragments after lithotripsy, it allows the intrarenal pressures to be controlled and kept in the lower range.

Antibiotic prophylaxis to prevent the onset of infectious complications after endourological stone treatments is widely used although only limited evidence from RCTs was retrieved (67).

Extension of oral antibiotic administration after intravenous perioperative prophylaxis, or administration of a course of antibiotic treatment in the days prior to surgery, does not seem to reduce the risk of infection in patients with low risk of infectious complications, (i.e., patients with negative preoperative urine culture and absence of hydronephrosis and urinary catheters).

However, in a study that considered patients with moderate/high risk of infectious complications, administration of a 10-day course of oral nitrofurantoin before the procedure in addition to intraoperative prophylaxis was shown to reduce the risk of infectious complications after PCNL.

EAU guidelines (63) state that there is no "*clear-cut evidence*" for prevention of infection following ureterorenoscopy and percutaneous stone removal, although a matched case control study demonstrated the efficacy of antibiotic prophylaxis to reduce infectious complications after PCNL in patients with negative baseline culture (68). Another study showed that a single dose administration was found sufficient to prevent post-ureteroscopic infections (69).

In conclusion, infectious complications after endourological treatment of kidney stones appear to depend (i) on the characteristics of the stone, on the patients' urinary tract, and on the patients' comorbidities.

The choice of a specific procedure for kidney stone treatment does not appear to be decisive for the onset of infectious complications, although the prevention of high intrarenal pressures during the procedure appears to be crucial in defining the risk of infectious complications. High intrarenal pressure depends on the modality of irrigation and on the use of the ureteral sheaths and suction systems to facilitate the outflow of urine. Antibiotic prophylaxis should be tailored to the characteristics of the stone and of the urinary tract, the history of the patient (comorbidities, previous UTI episodes) and the course of the procedure (operative time, method and volume of irrigation).

In high-risk cases, prudence is recommended, avoiding prolonged operating times, and administering antibiotic treatment before the procedure in adjunct to perioperative prophylaxis.

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