REVIEW ARTICLE

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Changes in male sexuality after urologic cancer: a narrative review

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ABSTRACT

Objective: To describe the most common sexual problems and changes experienced by male urological cancer survivors, focusing on evidence-based practices for assessment and intervention.
Materials and Methods: We search the PubMed, Embase, and SciELO databases between 1994 and 2022, using the following key words: "urological cancer", "urological malignances", "genitourinary cancer", "male sexual health", and "male sexual dysfunction".
Results: This narrative review provides an overview of the current literature involving the impact of diagnosis and treatment of urological cancers on male sexual function. Male "genital" or "reproductive" tumors, such as prostate, penile, and testicular tumors, clearly appear to affect sexual function. However, tumors that do not involve genital parts of the body, such as the bladder and kidney, can also affect male sexual function.
Conclusion: Male sexual dysfunction is very common after urologic cancer diagnosis and treatment. Changes in body image and anatomical damage can be associated with impaired masculinity and sexual function, especially after prostate, penile or testicular cancer treatment. Moreover, anxiety, depression, and fear of recurrence have an impact on quality of life and sexual function regardless of the cancer location. Therefore, patients need be counseled about the likely changes in sexual function before treatment of any urological cancer.

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INTRODUCTION

Sexual function is an important component of quality of life and can be adversely impacted by cancer and its treatment. Moreover, the fear of death, along with psychological and social factors, often deeply affects the quality of life of cancer patients (1).

Treatment of urological cancers can have especially significant impacts on sexual function, body image, well-being, and mental health (2, 3). Most studies of male sexual dysfunction after urologic cancer focus on prostate cancer (PCa) survival after surgical and hormonal treatments (4, 5). However, cancers that do not involve parts of the

body designated as ''sexual'' or ''reproductive'', such as kidney (KC) and bladder cancer (BC), can also affect sexuality independent of the treatment, and their relation to sexual function is poorly understood (6, 7).

Sexual function is a critical quality-of-life predictor and, as such, should be addressed during the treatment of all urological malignancies (8). Professionals working in this field should be aware of the impact of cancer on male sexuality. Therefore, it is important to address these topics in the urological literature. In this review, we describe the most common sexual problems and changes experienced by male urological cancer survivors, focusing on evidence-based practices for assessment and intervention.

MATERIAL AND METHODS

We analyzed published papers contained in the PubMed, Embase, and SciELO databases between 1994 and 2022, searching by the following key expressions: "urological cancer", "urological malignances", "genitourinary cancer", "male sexual health", and "male sexual dysfunction". Special emphasis was given to relevant articles reporting the changes in sexual health of men with urological cancers, such as prostate, penis, testicular, bladder, and kidney cancers. In this search, we included only papers published in English and excluded case reports, editorials, and opinions of specialists.

RESULTS

This narrative review provides an overview of the current literature involving the impact of diagnosis and treatment of urological cancers on male sexual function. Male "genital" or "reproductive" tumors, such as prostate, penile, and testicular tumors, clearly appear to affect sexual function. However, tumors that do not involve genital parts of the body, such as the bladder and kidney, can also affect male sexual function.

Prostate cancer (PCa)

PCa is the second most often diagnosed cancer among men worldwide (9). Different treatment modalities for PCa can negatively affect sexual function. Surgery is the reference standard for treatment of localized PCa. Nerve-sparing radical retropubic prostatectomy was developed many years ago to preserve sexual potency and urinary continence. Catalona et al. (10) evaluated the results of 1,870 open retropubic prostatectomies (ORP) performed by a single surgeon and found recovery of erectile function in 68% of preoperatively potent men treated with bilateral (543 of 798) and 47% treated with unilateral (28 of 60) nerve sparing surgery. Today, minimally invasive techniques such as laparoscopic radical prostatectomy (LRP) and robotic-assisted laparoscopic radical prostatectomy (RALP) have replaced ORP to improve post-operative outcomes such as erectile function (11). Guillonneau et al. (12) evaluated their experience with 550 patients who underwent LRP and found that 66% preserved erection and could engage in spontaneous intercourse. Patel et al. (13) analyzed the initial outcomes of 500 RALPs and found that after one year, 78% of patients were potent with or without the use of oral medications. More recently, Barisi et al. (4) conducted a systematic literature review comparing ORP, LRP, and RALP, where one of the outcomes was erection dysfunction (ED). According to this study, there were no differences in post-operative rates of ED between ORP and LRP or RALP. Interestingly, LRP was associated with greater post-operative rates of ED when compared with RALP. However, this review should be interpreted with caution due to the lack of randomized clinical trials, selection bias, and heterogeneous definitions of ED. In addition to ED, sexual changes after radical prostatectomy include loss of penile length, reduced sexual desire, and orgasmic dysfunction, including painful orgasm and climacturia, or involuntary loss of urine at the time of orgasm (14-16). True rates of climacturia are unknown and probably underreported in the literature (17). Clavell-Hernandez et al. (18) conducted a review of the literature on climacturia after radical prostatectomy and found prevalence ranging from 20% to 93%.

ED after radiotherapy (RT) usually occurs due to penile neurovascular and cavernosal damage. While ED is an immediate side effect of radical prostatectomy, it usually occurs after six months

post radiation therapy. Donovan et al. (5) report that only 22% of men-maintained erections firm enough for intercourse six months after RT with neoadjuvant androgen deprivation therapy (ADT). Likewise, Kikuchi et al. (19) evaluated erectile function after RT in 55 patients with PCa and observed a decrease in the erectile function and intercourse satisfaction after RT. Another study evaluated sexual functions of 50 PCa patients receiving RT. The authors used the IIEF (International Index of Erectile Function) questionnaire before and on the last day of treatment. They found a statistically significant decline in erectile function, sexual desire, sexual satisfaction, orgasmic function, and general satisfaction after RT. Considering that ED is usually chronic side effect of RT, these findings might reflect a psychological side effect of RT (20).

While radical treatment with surgery or radiation offers excellent cancer control, it comes with significant side effects as discussed previously. Alternative treatments with less impact in quality of life and sexual function have gained popularity in recent years.

Focal therapy (FT) is an a less invasive option that treats only the cancerous area of the prostate (aka index lesions) and maintains patient's quality of life by avoiding some of the adverse effects of radical therapy, including ED. Several studies with large sample size and long follow up showed benefits of FT on functional outcomes (21-24). Nahar et al. (22) reported short--term outcomes of FT for primary treatment of localized PCa and observed that sexual function returned to baseline at within 9-12 months. Similarly, Rischmann et al. (23) evaluated 111 patients with unilateral localized PCa treated with high intensity focused ultrasound (HIFU). Erectile function was preserved in 78% of patients after 12 months of HIFU half-gland treatment. A recent study compared the impact of focal (N = 195) and whole gland (N = 105) therapy for PCa on erectile and urinary function. Twelve months after treatment, 81.3% of men who underwent FT (vs. 61.7% of whole gland patients) could achieve erection strong enough for sexual penetration (24).

Similarly, Active surveillance (AS) is one the preferred choice for patients with low-risk prostate cancer. However, even men under AS can suffer negative impacts on sexual function. Soloway et al. (25) followed men in AS for PCa and observed 49% of patients experiencing ED. Another study compared the sexual function of men with low-risk PCa monitored through AS with patients undergoing RT or radical prostatectomy and found that the AS group had less ED (26).

Patients with metastatic prostate cancer are usually treated with androgen deprivation therapy (ADT) with the goal of reducing serum testosterone levels. Therefore, castration levels of testosterone results in multiple side effects, including loss of libido and ED. It's extremely important to correctly inform patients about these well-known side effects before starting treatment (27, 28).

Penile cancer (PEC)

PEC is rare in North America and Europe; the incidence is higher in regions of Africa, Asia, and South America due to due socioeconomic factors and the high incidence of the human papilloma virus (HPV), phimosis, and smoking in these regions (29-31). The treatment modalities of PEC depend on the area involved and include some organ-sparing treatments such as topical therapy, laser therapy, RT, glansectomy, wide-local excision, and partial penectomy. Total penectomy is reserved for cases with more advanced primary disease (32).

All types of treatment for PEC can impact quality of life and sexual function. Glansectomy seems to preserve sexual function by maintaining the ability to perform vaginal penetration and leaving libido and ejaculation function intact; however, the few studies available evaluating the results of the procedure had small sample sizes and several methodological flaws (33-35). Palminteri et al. (36) described the techniques and results of surgical reconstruction of glans penis lesions (benign, premalignant, and malignant). In their series, five cases were treated with glans resurfacing, five glansectomies with neoglans reconstruction were performed, and seven patients underwent partial penectomy and reconstruction of the neoglans. All patients maintained sexual function and activity. Patients who underwent glans resurfacing reported glandular sensory restoration while sensitivity was reduced after glansectomy and partial

penectomy. Partial or total penectomy can be associated with significant psychological morbidity and sexual dysfunction. Feelings of shame due to the small penis size and the absence of the glans are some reasons for the negative impact on male sexual function. In one such study, Romero et al. (37) investigated 18 patients who underwent partial penectomy and reported a statistically significant reduction in erectile and orgasmic function after surgery. According to the authors, only 33.3% of patients maintained their preoperative sexual intercourse frequency and were satisfied with their overall sex life after the procedure. Monteiro et al. (38) evaluated the erectile function of 81 patients who underwent partial penectomy and reported that approximately 62% experienced ED after surgery. The authors found that smaller penile shaft length, clinically positive lymph node, and older age significantly increased the incidence of ED. In the study conducted by Opjordsmoen et al. (39), four of 30 men treated for PEC underwent total penectomy, and all of them reported severely reduced global sexual score. Due to the rarity of PEC, there are few studies available exploring sexual outcomes after treatment. Although most of the papers are retrospective with a small sample, it is clear that an penile malignancies and treatments negatively impact patients' sexuality. Therefore, physicians should counsel patients with this rare malignancy about the impact and changes of male sexual function that they are likely to experience after PEC treatment. Referral to psycho-oncology might be beneficial to patients.

Testicular cancer (TC)

TC accounts for about 1% of all male cancers and characteristically affects mostly young men (aged 20–40 years). TC has a good prognosis with excellent cure rates in the early stages when treated by one of the standard treatment options, including orchiectomy, RT, and cisplatin-based chemotherapy (40, 41). Treatment of TC can cause changes in body image and negatively impact sexuality, fertility, mental health, and quality of life. An Australian study found that TC survivors experienced anxiety and depression in 19% and 20% of cases respectively (42). Rincones et al. (43) conducted a systematic review of anxiety, depression, fear of cancer recurrence and distress in TC survivors. The authors concluded that greater anxiety and depression seemed to be associated with impaired masculinity, sexual function, and quality of life. Changes in body image after orchiectomy can impact self-confidence and sexuality, and it is extremely important that physicians offer a testicular prosthesis implant at the time of surgery (44). A systematic review conducted by Nazareth et al. (45) of sexual dysfunction in men treated for TC indicated significantly reduced or absent orgasm and ejaculatory dysfunction that persisted for up to two years after treatment. Not surprisingly, ejaculatory dysfunction was most frequently related to retroperitoneal lymph node dissection (RPLND) surgery (46). Palotti et al. (47) evaluated the possible effect of TC and orchiectomy on sexual function. They administered the IIEF-5 to TC patients at the post-orchiectomy baseline before chemotherapy and found that 37.7% of patients had ED. According to the authors, the sexual dysfunction in these patients might be associated with psychological burden. In fact, sexual dysfunction in TC is not clearly related to disease or treatment factors and may instead arise from psychological vulnerability (46).

Bladder cancer

Bladder cancer (BC) is the fifth most common cancer in men worldwide (48). Most patients have non-muscle-invasive bladder cancer (NMIBC), which is commonly treated with transurethral resection of bladder tumor (TURBT). There is scarce research on the effect of treatment for NMIBC on male sexual function. Existing research suggests that TURBT may adversely affect male sexuality and lead to anxiety and depression, especially in younger patients (49). Guo et al. (7) investigated the incidence of ED in patients before and after TURBT to treat NMIBC. According to the authors, the incidence of ED increased in patients under the age of 45 years after TURBT (15.8% before vs. 52.6% after), and they concluded that psychological and emotional burden are the main causes of sexual dysfunction in these cases. Yoshimura et al. (50) prospectively evaluated the impact on general health-related quality of life of patients with NMIBC who underwent TURBT. They found

physical and mental problems after the first TURBT, but these problems gradually waned as TURBT was repeated, although the patients' general quality of life remained affected. More than a half of NMIBC cases will recur and intravesical bacille Calmette–Guérin (BCG) treatment has an important role in reducing this recurrence (51). Patients who received intravesical BCG might present with pelvic pain and may experience a negative impact on sexual activity after the initial treatment. Nonetheless, patients improved their psychological distress and physical symptoms as they continued the treatment (52, 53). ED after BCG treatment is generally transient and reversible but is still another source of psychological distress (54). Radical cystectomy (RC) remains the gold standard treatment in cases of muscle invasive bladder cancer (MIBC). It consists of removal of the bladder, prostate, and seminal vesicles (55). ED after RC is a prevalent problem due to surgical trauma to the neurovascular bundle, and one study found that only 14% of sexually active men-maintained potency after surgery (56). However, nerve-sparing RC can often provide preservation or recovery of erectile function, and 36% of RC patients recovered sexual intercourse at 3 years and 57% at 5 years. This recovery depends on the preoperative erectile function and age of the patient. Function can be improved after sexual rehabilitation with intracavernous injection therapy or oral phosphodiesterase inhibitors after surgery (57, 58). The type of urinary diversion can also affect sexual activity. Patients with ileal conduit diversion may have a greater impact on sexual function compared to those who underwent orthotopic diversion likely due to depression or anxiety associated with changes in body image (59). Trimodality therapy (TMT) can be used as an alternative to immediate RC in the management of MIBC. TMT consists of maximal TURBT followed by radical RT with concurrent chemotherapy (60). Radical RT for BC can result in sexual dysfunctions such as impotence and lack of desire (61). Zietman et al. (62) performed a small retrospective study of TMT and found male sexual function to be less impaired by this modality than after RC. A total of 39% of men reported no erections in the last 4 weeks, 54% were capable of orgasm and 50% of ejaculation, while only 8% were dissatisfied with their sex lives.

Kidney cancer (KC)

KC incidence is increasing, and over 50% of KC tumors are diagnosed incidentally in asymptomatic individuals during investigation for other conditions using imaging techniques (63, 64). The literature is scarce about the impact on male sexual function after treatment for KC. Anastasiadis et al. (65) published the first study addressing sexual function in patients with KC after treatment (operation, radiation, or chemotherapy). They observed that most patients remained sexually active in non-distressed relationships, but 51% of men reported depressive symptoms, and sexual functioning may be worse than in comparable chronically ill populations. Christiansen et al. (6) evaluated patients who underwent nephrectomy or nephroureterectomy and found that 54.7% of sexually active males reported having some degree of ED after surgery. Moreover, 61% of patients reported being worried about their sex lives. Interestingly, only 5% of patients were informed about these potential negative effects prior to surgery. Few studies have investigated sexual disorders in men with advanced KC treated with molecular targeted therapy (MTT); antiangiogenic therapies (sunitinib, sorafenib, and bevacizumab) and mTOR inhibitors (temsirolimus and everolimus) caused a decline of erectile function scores and sexual activity after treatment (66, 67). These studies concluded that treatment of KC can negatively affect male sexual function. The diagnosis of cancer, life stress, and losses can explain the sexual dysfunction after treatment, which is information that should be provided to patients (1, 68). Table-1 summarizes the risk of ED after type of urologic cancer treatment.

CONCLUSIONS

Male sexual dysfunction is very common after urologic cancer diagnosis and treatment. Changes in body image and anatomical damage can be associated with impaired masculinity and sexuality, especially after PCa, PEC, or TC treat-

ment. Moreover, anxiety, depression, and fear of recurrence have an impact on quality of life and sexual function even in "nonreproductive" cancers, such as BC and KC.

Therefore, patients need be counseled about the likely changes in sexual function before treatment. Urologists and oncologists should systematically inform, educate, and comfort these patients during the treatment. Multidisciplinary medical teams, including sexual medicine physicians and psycho-oncologist, play a fundamental role in this scenario and need to be proactive by offering psychological support to mitigate the impact on male sexuality. However, more studies are needed to clarify the impact urological malignances and their treatments may have on the sexual function of men, and clinicians need better training about the best way topproach these issues.

Table 1 - Risk of ED after type of urologic cancer treatment.

Study	Year	Treatment	Risk of ED
Catalona et al. (10)	1999	ORP	32%
Guillonneau et al. (12)	2002	LRP	34%
Patel et al. (13)	2007	RALP	22%
Donovan et al. (5)	2016	RDT + NEOADJUVANT ANDROGEN THERAPY	78%
Borges et al. (24)	2021	FOCAL HIFU	18%
Soloway et al. (25)	2010	AS	49%
Monteiro et al. (38)	2021	PARTIAL PENECTOMY	62%
Guo et al. (7)	2022	TURBT	56%
Palotti et al. (47)	2019	ORCHIETOMY	37%
Zippe et al. (26)	2004	RC	86%
Miyao et al. (57)	2001	NERVE-SPARING RC	43%
Zietman et al. (62)	2003	TMT	39%
Christiansen et al. (6)	2020	NEPHRECTOMY OR NEPHRO-URETERECTOMY	54%

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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One week pre-operative oral antibiotics for percutaneous nephrolithotomy reduce risk of infection: a systematic review and meta-analysis

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ABSTRACT

Purpose: The aim of this meta-analysis is to assess the efficacy of extended dose of preoperative antibiotics to reduce infectious risk in patients undergoing percutaneous nephrolithotomy (PCNL).

Materials and Methods: A literature search for prospective case-control studies or randomized controlled trials was done. PICO framework was used. Population: adult patients that underwent to PCNL; Intervention: extended dose preoperative antibiotic prophylaxis before PCNL; Control: short dose preoperative antibiotic prophylaxis before PCNL; and Outcome: systemic inflammatory response syndrome (SIRS) or sepsis, fever after PCNL and positive intraoperative urine and stone culture. This meta-analysis was registered in PROSPERO database under the number: CRD42022359589.

Results: Three RCT and two prospective studies (475 patients) were included. SIRS/sepsis outcome was retrieved from all studies included. Seven days preoperative oral antibiotics for PCNL was a protective factor for developing SIRS/sepsis (OR 0.366, 95% CI 0.234 - 0.527, p < 0.001). There was no statistical association between seven-day use of antibiotics and fever (OR 0.592, 95% CI 0.147 – 2.388, p = 0.462). Patients who received seven days preoperative antibiotics had lower positive intraoperative urine culture (OR 0.284, 95% CI 0.120 – 0.674, p = 0.004) and stone culture (OR 0.351, 95% CI 0.185 – 0.663, p = 0.001) than the control group.

Conclusion: one week of prophylactic oral antibiotics based on local bacterial sensitivity pattern plus a dose of intravenous antibiotics at the time of surgery in patients undergoing PCNL reduces the risk of infection.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the current gold standard treatment for kidney stones > 20 mm (1). Although effective, PCNL is associated with complications such as prolonged urinary leakage in up to 10% and blood transfusion in up to 7% of the patients (2-5). Approximately 10% of the patients develop a postoperative fever after PCNL, while sepsis is reported in 0.3% to 0.5% (5, 6). Despite being rare, urosepsis is a life-threatening complication of PCNL, and every

effort should be made to prevent its occurrence.

There is no specific recommendation for a preoperative antibiotic regimen in patients undergoing PCNL due to insufficient data (1, 7). Previously published meta-analyses evidenced significant heterogeneity between included studies. Retrospective and prospective studies were analyzed together, preoperative, and postoperative antibiotic regimens were compared in the same meta-analysis, and duplicates were included making it impossible to determine the role of preoperative antibiotics(8-10). There is no consensus on the definition of high infectious risk patients. Several possible risk factors for infection were investigated. Patient positioning in PCNL, tract size, obesity and solitary kidney do not seem to impact infectious rates (11-14). Some investigators consider high risk for infection stone size ≥ 20 mm and/or dilation of the collecting system with sterile urine. However, other authors define high infectious risk for PCNL as those with a positive preoperative urine culture within three months of the planned procedure or an indwelling stent or nephrostomy tube at the time of surgery, without considering stone size or dilation of the collecting system (15-17). As the definition of high infection risk is unclear, this study aims to perform a high-quality meta-analysis using only prospective studies to define the role of preoperative antibiotics in patients undergoing PCNL.

MATERIALS AND METHODS

Identification and Eligibility of Trials

The meta-analysis protocol was registered on the PROSPERO database on September 22, 2022 (CRD42022359589). This review was conducted according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement (18). We selected prospective studies and randomized controlled trials (RCT) that compared extended to short-dose preoperative antibiotic prophylaxis in patients undergoing PCNL. On May 2022, the key words "percutaneous nephrolithotomy" and "antibiotic" were searched on EMBASE, PubMed, and Web of Science platforms. Retrospective studies, case reports, case-control studies, letters to the editor, editorials, congress abstracts, and studies in patients < 18 years old were excluded.

Development of Prospective Meta-analysis Protocol

The PICO (population, intervention, control, and outcome) framework was agreed upon before the collection of data:

- Population: adult patients that underwent PCNL;
- Intervention: extended dose preoperative antibiotic prophylaxis before PCNL;
- Control: short dose preoperative antibiotic prophylaxis before PCNL; and
- Outcome: systemic inflammatory response syndrome (SIRS) or sepsis, fever after PCNL, positive intraoperative urine culture, and stone culture.

Outcomes and Comparisons

The primary outcome measure was SIRS or sepsis after PCNL. Primary comparison investigated extended dose preoperative antibiotic prophylaxis vs. short dose preoperative antibiotic prophylaxis before PCNL. Secondary outcome measures investigated included fever after PCNL, positive intraoperative urine, and stone cultures. We considered extended dose the use of preoperative antibiotics for seven days before PCNL and short dose for ≤ 2 days. SIRS or sepsis were defined according to each study (19, 20).

Assessment of risk of bias in included studies

Risk of bias assessments were done independently by two of the investigators with agreement, without discrepancy. The risk of bias for each RCT was assessed using version 2 of the Cochrane Risk of Bias Assessment Tool (RoB 2). RoB 2 is structured into domains of bias (trial design, conduct, and reporting results) and classified as unclear, low, and high risk (21). The risk of bias for each prospective study was defined using The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I), recommended by the Cochrane Scientific Committee. ROBINS-I is structured into the selection of patients, conduct, and reporting results and is classified as low, moderate, serious, and critical risk (22).

Data Analyses

All analyses were performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). The primary outcome was extracted from all included studies. Secondary outcomes were not available in all studies. We calculated each study's odds ratio (OR) and 95% confidence interval (CI) to evaluate their differences. Chi-squared test and I2 were used to assess heterogeneity. When heterogeneity was present, the random effects model was used. The alpha risk was defined as < 0.05.

RESULTS

Search results and selection process

As shown in Figure-1, literature search identified 1362 publications. Abstracts and titles were screened, excluding all studies that were not prospective or RCT. After full-text screening, eight articles were selected, and three were excluded (another outcome evaluated, and duplicated database). The final selection included five articles (three RCT and two prospective studies) with a total of 475 patients studied.

Risk of bias

As shown in Figure-2, Bag 2011, Chew 2018, and Sur 2021 were considered to have a low risk of bias in all criteria according to RoB 2 (16, 17, 23). Mariappan 2006 and Xu 2022 were considered to have some moderate/serious risk of bias according to ROBINS-I (15, 24). Xu 2022 did not have specific criteria for antimicrobial choice – "antibiotics (type and duration) were given at the discretion of the surgeon; the urine culture took 48-72h, and some patients did not get the results before the procedure" (24).

Characteristics of included studies

Mariappan et al. 2006 were the first to demonstrate in a prospective study that one week of

Figure 1 – PRISMA flowchart.

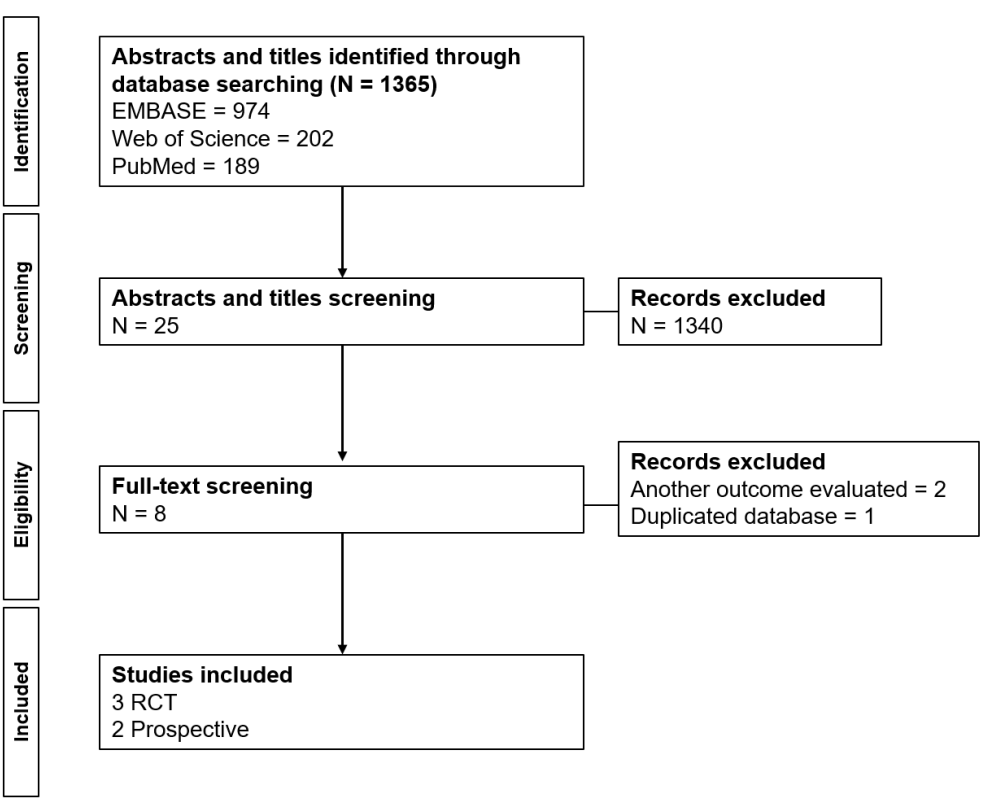
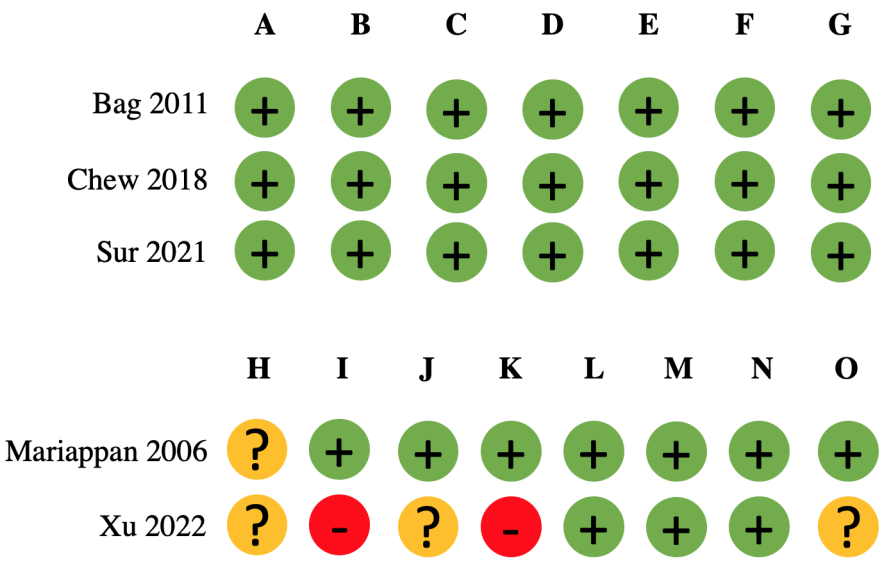


Figure 2 - Risk of bias of randomized controlled trials.



(A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias); (G) Other bias; (H) Bias due to confounding; (I) Bias in selection of participants into the study; (J) Bias in classification of interventions; (K) Bias due to deviations from intended interventions; (L) Bias due to missing data; (M) Bias in measurement of outcomes; (N) Bias in selection of the reported result; (O) Overall bias.

antibiotics in patients with high infectious risk undergoing PCNL reduces urosepsis. Results showed a three times less chance of urosepsis in patients receiving antibiotics one week before intervention (RR 2.9; 95% CI 1.3-6.3, p = 0.004)(15).

Bag et al. demonstrated in a RCT of 110 patients with stones ≥ 25 mm or hydronephrosis undergoing PCNL that prophylaxis with nitrofurantoin 100 mg twice daily for a week before PCNL prevents urosepsis and fever. Results showed that patients using nitrofurantoin had less SIRS (19% vs. 49%, OR 0.31, p = 0.01), less positive pelvic urine culture (0 vs. 9.8%, RR 4.95, p = 0.001), and less positive stone culture (8.3% vs. 30.2%, OR 0.22, p = 0.016) (16).

The EDGE Consortium reported two multicenter RCTs addressing preoperative oral antibiotics in patients undergoing PCNL. Chew et al. conducted a RCT with patients with sterile preoperative urine cultures and no urinary drains, which was deemed "low risk." There was no difference in the incidence of sepsis (12 vs. 14%, p = 1.0), fever (0 vs. 2.3%, p = 0.24), positive intraoperative renal pelvis urine culture (9.3 vs. 9.3%, p = 1.0) and positive stone culture (2.3 vs. 2.3%, p = 1.0) between antibiotic and control groups (23). In the EDGE Consortium's subsequent publication, Sur et al. demonstrated that seven days vs. two days of preoperative 100 mg nitrofurantoin twice daily decreases the risk of urosepsis in moderate to high infectious risk patients undergoing PCNL. Both groups received intravenous antibiotics at the induction of the procedure. It was observed that patients who received two days of antibiotics had a higher risk of sepsis (OR 3.1, 95% CI 1.1 - 8.9, p = 0.031) (17).

Xu et al. 2022 (24), prospectively studied the optimal duration of preoperative antibiotic therapy was prospectively studied in consecutive patients with positive urine culture submitted to PCNL. In this "real-world" study, authors concluded that ≥ 7 days of antibiotics before procedure in high infectious risk patients reduces the risk for urosepsis. A significant limitation of this study is that a wide range of antibiotics was used according to sensitivity test of positive urine culture of patients undergoing the procedure. We managed to extract data from patients that used single-dose

(28 patients) vs. seven-day (30 patients) antibiotics before PCNL to include in our meta-analysis. It was evidenced that receiving antibiotics seven or more days before the procedure was a protective factor independently associated with SIRS (24) (Table-1).

Outcomes

SIRS/sepsis outcome was retrieved from all studies included. Postoperative fever outcome was extracted from three studies. Intraoperative urine culture and stone culture outcomes were extracted from four and three studies, respectively. Funnel plots demonstrating studies' bias and heterogeneity are shown in Figure-3. Forest plots (Figure-4) evidenced that using antibiotics for seven days in the preoperative period of PCNL was a protective factor for developing SIRS/sepsis (OR 0.366, 95% CI 0.234 - 0.527, $p < 0.001$). There was no statistical association between the seven-day use of antibiotics and fever (OR 0.592, 95% CI 0.147 – 2.388, $p = 0.462$). Patients who received the intervention had lower positive intraoperative urine culture (OR 0.284, 95% CI 0.120 – 0.674, $p = 0.004$) and stone culture (OR 0.351, 95% CI 0.185 – 0.663, $p = 0.001$) than the control group.

DISCUSSION

This meta-analysis shows that seven days of oral preoperative antibiotics plus a dose of intravenous antibiotics at the time of surgery reduces the risk of infection in patients undergoing PCNL. Extended preoperative antibiotic use reduced the risk of SIRS and positive intraoperative urine culture and stone culture, regardless of the patient's risk of infection. Due to a lack of consensus in defining high infectious risk patients for PCNL, this meta-analysis included all adult patients undergoing PCNL. Our meta-analysis included only studies that investigated preoperative and not postoperative use of antibiotics to avoid confounding timing in antibiotics use in patients undergoing PCNL. The previous meta-analysis joined studies of preoperative and postoperative use of antibiotics, reducing its clinical application (8).

Nowadays, sepsis definition is as a life-threatening organ dysfunction caused by a dysregulated host response to infection (25). However, in the past, sepsis was described as a systemic inflammatory response syndrome (SIRS) to infection (19). In some studies, researchers referred to urosepsis as SIRS resulting from infection in the urinary tract in patients undergoing PCNL. Mariappan et al. and Bag et al. considered SIRS as fever > 38° C and/or leukocyte counts > 12,000 and attributed to urosepsis after excluding perinephric collection, pleural effusion, chest infection, and thrombophlebitis (15, 16). The EDGE Consortium used the more current definition of sepsis, which includes two or more of the following criteria at least 12 hours after the procedure: temperature above 38.3°C or below 36°C, heart rate above 90/minute, respiratory rate greater than 20/minute, altered mental status, systolic blood pressure less than 90 mmHg, mean arterial pressure less than 70 mmHg or systolic blood pressure decrease of more than 40 mmHg, and white blood cells greater than 12,000 or less than 4,000 (17, 23). Despite the definition used at the time of performance of the study, researchers investigated whether preoperative antibiotics could prevent infection, and the incidence of this event was similar between studies. This was the main reason we maintained the definition of sepsis in each original study.

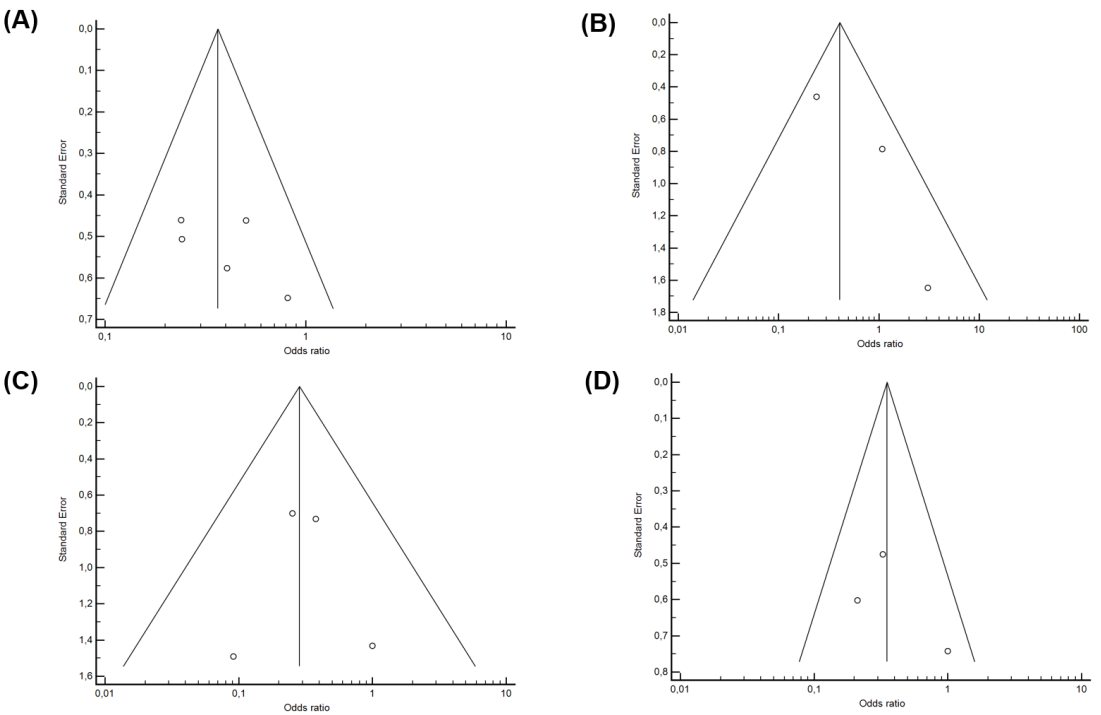
We choose to include in this meta-analysis adult patients undergoing PCNL regardless of their risk of infection. The definition of high infectious risk patients for PCNL varies among studies and is controversial. Patients with sterile urine and dilated pelvicalyceal systems and/or stones of ≥ 20 mm were considered at high infectious risk by Mariappan et al. based on a previous publication from their group (26). Other authors considered sterile urine, hydronephrosis, and/or stones ≥ 25 mm high risk (16). However, it is unclear if those patients had positive urine culture weeks before PCNL and were treated. In contrast to Mariappan et al. and Bag et al., stone size or dilated collecting system were not considered risk factors in the Sur et al. study. A previous RCT of the EDGE group did not demonstrate a benefit for the preoperative use of nitrofurantoin for seven days in patients with sterile urine and no urinary drain undergoing PCNL (23). Therefore, EDGE Consortium created a definition of moderate to high infectious risk pa-

Table 1 - Description of included studies.

Study	Country	Design	Inclusion criteria	Definition of SIRS or Sepsis	Procedure	Patients, n	Mean age, years	Stone size, mm
Mariappan, et al. 2006 (15)	UK	Prospective	Stones ≥ 20 mm and/or dilated pelvicalyceal system	SIRS was defined as the systemic response to infection, manifested by two or more of the following conditions as a result of infection: - Temperature ≥ 38º C or ≤ 36º C - Heart rate > 100 beats/min - Respiratory rate > 20/min - White blood cell count > 12,000 white blood cells/mL or < 4,000 white blood cells/mL	7 days of antibiotic (250 mg of ciprofloxacin twice daily) before PCNL vs. No antibiotic before PCNL	52 vs. 46	55.5 vs. 53.1	30.8 vs. 32.8
Bag et al. 2011 (16)	India	RCT	Patients with stones ≥ 2,5 cm and/or hydronephrosis and sterile urine	Hard criteria for SIRS were fever > 38º C and/or leukocyte counts > 12,000	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. No antibiotic before PCNL	48 vs. 53	39.2 vs. 40.4	34.1 vs. 36.7
Chew et al. 2018 (23)	USA/ Canada	RCT	Patients with sterile urine and no urinary drain	Sepsis was defined as having an infection source in addition to 2 or more of the following criteria at least 12 hours after the procedure: temperature > 38,3ºC or < 36ºC, heart rate > 90/minute, respiratory rate > 20/minute, altered mental status, systolic blood pressure < 90mmHg, mean arterial pressure decrease of more than 40 mmHg and white blood cell count > 12,000 or < 4,000.	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. No antibiotic before PCNL	43 vs. 43	56 vs. 62	19 vs. 17
Sur et al. 2021 (17)	USA/ Canada	RCT	Patients ≥ 18 years old who had stone burden of any size for which PCNL was recommended. Subjects had to have had either a positive preoperative urine culture within 3 months of the planned procedure or an internalized ureteral stent, nephrostomy tube or nephroureteral stent at time of PCNL.	Sepsis was defined as having an infection source in addition to 2 or more of the following criteria at least 12 hours after the procedure: temperature > 38,3ºC or < 36ºC, heart rate > 90/minute, respiratory rate > 20/minute, altered mental status, systolic blood pressure < 90mmHg, mean arterial pressure decrease of more than 40 mmHg and white blood cell count > 12,000 or < 4,000.	7 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL vs. 2 days of antibiotic (100 mg of nitrofurantoin twice daily) before PCNL	68 vs. 55	61 vs. 54	20 vs. 23
Xu et al. 2022 (24)	China	Prospective	Patients with positive urine culture undergoing primary PCNL	SIRS was defined as the co-existence of at least two of the following items during the whole hospitalization: temperature > 38ºC or < 36ºC, heart rate > 90/min, respiratory rate > 20/min or PaCO2 < 32 mmHg, and white blood cell count > 12,000 or < 4,000.	7 days of empiric antibiotic before PCNL vs. No antibiotic before PCNL	30 vs. 28	NA	NA

SIRS = systemic inflammatory response syndrome; PCNL = Percutaneous Nephrolithotomy; RCT = randomized controlled trials; NA = not available

Figure 3 – Funnel plot – (A) patients with SIRS or sepsis; (B) patients with fever; (C) positive intraoperative urine; (D) positive stone culture.



tients with a positive preoperative urine culture within three months of the planned procedure or an internalized ureteral stent, nephrostomy tube, or nephro-ureteral stent at the time of surgery (17). Xu et al. considered patients receiving antibiotic treatment for a positive urine culture, regardless of stone size, as high infectious risk patients for PCNL (24).

It was consensual amongst investigators that the choice of which antibiotic to use preoperatively in patients undergoing PCNL should be based on local bacterial sensitivity patterns (15-17, 23, 24). Mariappan et al. chose ciprofloxacin, while Bag et al., Chew B et al., and Sur et al. chose nitrofurantoin (15-17, 23). Although the level of bacterial resistance to nitrofurantoin is low, it is essential to note that nitrofurantoin has poor penetration into the tissues, and *Proteus sp*. and *Pseudomonas sp*. have inherited chromosomal resistance to it (27-29).

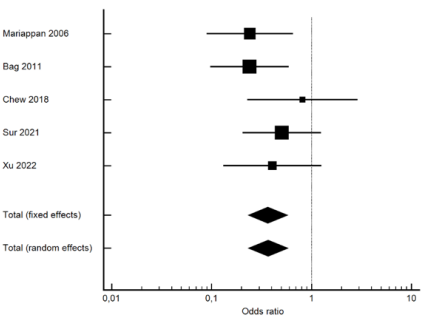
This meta-analysis demonstrated the protective role of one week of preoperative oral antibiotics for patients undergoing PCNL. Still, we recognize limitations, including a low number of subjects, heterogeneity of definitions of sepsis, and antibiotic use. The low number of participants is explained by our strict inclusion criteria of only prospective or randomized controlled trials in this meta-analysis. Nevertheless, the quality of a meta-analysis depends on the quality of the original studies included. As we aimed to investigate whether an intervention could reduce the risk of a serious complication, it was essential to have only prospective data due to its reliability and to minimize selection and report bias (30). Retrospective studies tend to underreport complications compared to their prospective counterparts. The definition of sepsis is an ongoing process, and we choose to keep the author´s definition at the time of the performance of the study. It is impossible to define the best prophylactic antibiotic based on this meta-analysis. Although the antibiotic used varied among studies, authors preferred ciprofloxacin or nitrofurantoin based on local bacterial flora.

Figure 4 – Forest plot – (A) SIRS or sepsis in control vs. intervention; (B) fever in control vs. intervention; (C) positive intraoperative urine culture in control vs. intervention; (D) positive stone culture in control vs. intervention.

(A)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	18	46	7	52	20.8%	0.242 (0.0897 – 0.653)
Bag 2011	26	53	9	48	25.2%	0.240 (0.0971 – 0.591)
Chew 2018	6	43	5	43	12.7%	0.811 (0.228 – 2.890)
Sur 2021	14	55	10	68	25.1%	0.505 (0.204 – 1.248)
Xu 2022	12	28	7	30	16.1%	0.406 (0.131 – 1.256)
Total	76	225	38	241	100%	0.368 (0.234 – 0.579)*

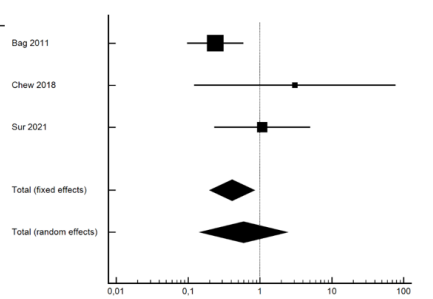
* p < 0.001; Test for heterogeneity: Chi2 = 3.5401, DF = 4, p = 0.4718, I2 = 0% (0.0 – 77.88).



(B)

	Control		Intervention		Weight (random events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Bag 2011	26	53	9	48	49.9%	0.240 (0.0971 - 0,591)
Chew 2018	0	43	1	43	14.4%	3.071 (0.122 – 77.504)
Sur 2021	3	55	4	68	35.7%	1.083 (0.232 - 5.059)
Total	29	151	14	159	100%	0.592 (0.147 – 2.388)*

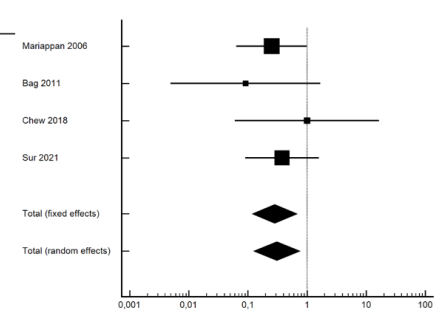
* p = 0.462; Test for heterogeneity: Chi2 = 4.3786, DF = 2, p = 0.1120, I2 = 54.32% (0.0 – 86.93)



(C)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	9	46	3	52	42.0%	0.252 (0.0637 – 0.995)
Bag 2011	5	53	0	48	9.3%	0.0909 (0.00489 – 1.690)
Chew 2018	5	53	0	48	10.1%	1.000 (0.0605 – 16.522)
Sur 2021	6	55	3	68	38.6%	0.377 (0.0898 – 1.582)
Total	21	197	7	211	100%	0.284 (0.120 – 0.647)*

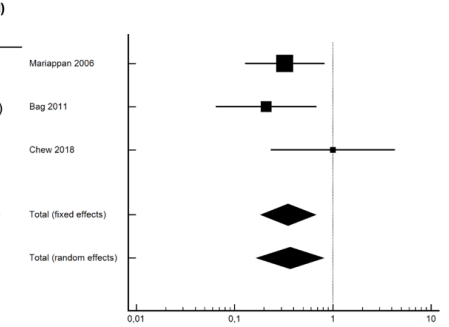
* p = 0.004; Test for heterogeneity: Chi2 = 1.5370, DF = 3, p = 0.6738, I2 = 0% (0.0 – 74.80)



(D)

	Control		Intervention		Weight (fixed events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Mariappan 2006	18	46	9	52	49.2%	0.326 (0.128 – 0.826)
Bag 2011	16	53	4	48	30.4%	0.210 (0.0646 – 0.684)
Chew 2018	4	43	4	43	20.1%	1.000 (0.233 – 4.286)
Total	38	142	17	143	100%	0.351 (0.185 – 0.663)*

* p = 0.001; Test for heterogeneity: Chi2 = 2.7390, DF = 2, p = 0.2541, I2 = 26.98% (0.0 – 97.55)



CONCLUSIONS

We conclude that one week of prophylactic oral antibiotics based on local bacterial sensitivity pattern plus a dose of intravenous antibiotics at the time of surgery in patients undergoing PCNL reduces the risk of infection. To optimize preoperative antibiotic use, more prospective data are needed to define better which patients are at a higher risk of infection after PCNL.

CONFLICT OF INTEREST

None declared.

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