Barretos Cancer Hospital

Antibiotic prophylaxis in urinary tract clearance by percutaneous nephrostomy and catheter changes in patients with malignant ureteral obstruction: Retrospective cohort study and systematic review with meta-analysis

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1. INTRODUCTION

1.1. Understanding ureteral obstruction

Ureteral obstruction can be caused by stones, infectious scars, trauma, congenital abnormalities, surgery, and also by malignant diseases [1] . The prevalence of malignant ureteral obstruction ranges from 21% to 82% in case series reported in the literature [1, (2)] .

It occurs when there is invasion or extrinsic compression of the ureter by the tumor mass or by metastatic lymph nodes present in the pelvis, around the ureters or in the retroperitoneum [1, 3(,) (4)] , causing partial or total occlusion of this ureter, which can result in acute kidney injury, the mortality of which is between 53% and 93% in severe cancer patients [5] . Malignant ureteral obstruction is responsible for around 7% of all causes of acute kidney injury in cancer patients [(6)] .

The main types of neoplasms responsible for ureteral obstruction are prostate cancer [7-10] , bladder cancer [7-9] , cervical cancer [7, 9-11] , ovarian cancer [7(,) (10)(,) (11)] and colon-rectal cancer [8-11] because they are anatomically close to the urinary tract.

Generally, malignant ureteral obstruction is caused by an advanced or progressing neoplastic disease, commonly associated with metastases, bringing with it a worse prognosis [12] . However, if clearance is not achieved, the threat to life is imminent [2, 7, (13)] .

1.2. Clearing the urinary tract

Urinary tract clearance is the treatment indicated to stop the high pressure inside the urinary tract and restore renal function, ensuring the continuity of cancer treatment or relieving uremic symptoms in more advanced diseases [2, (13)] .

The techniques and procedures to be used for such clearance include percutaneous nephrostomy, the passage of ureteral catheters (double-J catheter, internal-external catheter or metal catheter) and ureteral shunts (nephrocutaneous *by-pass*, cutaneous ureterostomy, transuretero-ureterostomy or Bricker ileal conduit), with these ureteral shunts being the last choices in palliative care as they are more invasive

procedures causing greater associated morbidity for patients with advanced neoplastic disease [12].

The choice of method will depend on the stage of the disease, the patient's clinical conditions and the pelvic anatomical alteration caused by the neoplasm, always considering the least invasive technique with the least interference in the local anatomy, such as the passage of the double-J catheter [14, 15].

However, percutaneous nephrostomy assumes its importance if the ascension of any type of catheter through the urinary tract is made impossible by the presence of a bladder tumor, local extrinsic compressions and even fistulas and hemorrhages [7, 12, 15].

1.3. About percutaneous nephrostomy

It was first described in 1955 as the insertion of a plastic tube into the renal pelvis (the funnel-shaped structure that drains the urine produced by the kidney into the adjoining ureter) after X-rays with contrast medium to draw this pelvis (antegrade pyelography) in patients with ureteral obstructions and undergoing urine drainage by lumbar puncture [16]. In 1974, ultrasound was used to guide this procedure, making it safer [17].

The main indication is for urinary tract clearance of benign or malignant origin, with or without infection (72% to 97% of all indications). It can also be used to control and treat ureteral fistulas and hemorrhagic cystitis (1% to 34% of all indications) and for diagnostic tests and access for therapeutic interventions (2% to 50% of all indications) [18, 19]. Relative contraindications include severe uncontrolled coagulopathies (risks of renal hemorrhage) and terminal illness / imminent death, as it becomes an unnecessary and futile procedure [18].

Percutaneous nephrostomy catheters can be used until the obstruction of the urinary tract is resolved by surgery, chemotherapy or radiotherapy, preventing kidney damage and allowing recovery of kidney function. They can also be used as a permanent palliative option in patients with advanced and/or untreatable neoplastic disease [19].

Success rates range from 84% to 99%, being lower in undilated urinary collecting systems, complex calculous disease and coralliform calculi, but with rates of 96% to 100% in obstructed urinary tracts with or without calculi [20]. Even so, percutaneous nephrostomy is not a complication-free procedure.

1.4. Complications related to percutaneous nephrostomy

The International Society of Interventional Radiology classifies complications based on results into minor and major complications (Appendix I) [21].

The complications inherent in this procedure occur in around 10% of patients with both benign and malignant diseases [18]. However, the figures can reach 29% (when only ureteral lithiasis is studied) [22].

1.4.1. Minor complications

There are reports of a 3% to 28% prevalence of minor complications [23, 24], with spontaneously resolving hematuria accounting for 13.2% to 18.9% [22,23,25]; pain occurs in 25% of cases [22] and catheter migration ranges from 12% to 17% [10,22

1.4.2. Major complications

One study found no major complications (death, hematuria requiring surgical management or blood transfusion, vascular laceration, pseudoaneurysm or arteriovenous fistula, infection requiring surgical management, sepsis or puncture of adjacent organs such as colon, spleen or lung) [24]. However, a non-systematic review reports the following rates of these complications [18]:

a) Individual complications that resulted in unexpected transfer to an intensive care unit, emergency surgery or prolonged hospital stay: 1% to 7%;

b) Pleural complications (pneumothorax, empyema, hydrothorax, hemothorax): 0.1% to 0.6%;

c) Intestinal perforation: 0.2% to 0.5%;

d) Vascular injury requiring embolization or nephrectomy: 0.1% to 1%;

e) Bleeding requiring blood transfusion: 1% to 4%;

f) Septic shock due to pyelonephritis: 7% to 9%;

g) Septic shock (fever, chills with hypotension, requiring a higher level of care): 1% to 10%.

1.4.3. Infectious complications

Even though the aforementioned review showed rates of pyelonephritis and septic shock related to percutaneous nephrostomy of up to 10%, the proportions of infectious complications can vary in the literature:

a) without evidence of urinary infections [23, (24)];
b) 8.5% of catheter insertion site infections [(25)];
c) 10.3% of intra-renal or peri-renal abscesses [(25)];
d) 3.7% to 15% of febrile episodes [11, 14, (26)];
e) 11.6% to 38.1% urinary tract infection [7, 9(,) (10)(,) (19)];
f) 7% of infections related to percutaneous nephrostomy [(27)];
g) 3.8% to 19% pyelonephritis [3, 14] and
h) 9% to 50% septicemia [9, (22)].

In studies of patients undergoing percutaneous nephrostomy for malignant ureteral obstruction alone, catheter-related urinary infection ranged from 3.8% to 38.1% [3, 7(,) (9)(,) (10)(,) (14)(,) (19)(,) (25)].

These disparate values exist because there is no robust clinical evidence on the best way to diagnose nephrostomy catheter-related urinary tract infection, especially in cancer patients, i.e. the definitions used in the studies are methodologically varied [(19)].

Of the proportions of urinary infection cited above, seven studies do not methodologically define nephrostomy catheter-related urinary tract infection [7, 9(,) (10)(,) (23-25)]. One study defines urinary infection as fever and flank pain accompanied by bacteriuria or pyuria with no other focus, but does not mention uroculture and time after procedure [14]. Another study defines an infectious complication only as fever (temperature greater than 38ºC) within 30 days of follow-up [26]. A third study defines temperature as less than 36ºC or greater than 38ºC, associated with a white blood cell count greater than 10,000 cells/mL, positive uroculture and blood culture [(27)].

Bahu *et al*. defined pyelonephritis as at least 1 sign or symptom (fever greater than 38ºC, pain on costovertebral percussion and/or flank pain) associated with uroculture with growth of no more than two species of microorganisms greater than or equal to 10^5 CFU/ml at 90-day follow-up after the procedure [3]. Szvalb *et al.* define infection related to percutaneous nephrostomy as any clinical symptom (fever, chills, pain on costovertebral percussion, hypotension and/or cellulitis at the catheter entry site) not explained by another diagnosis associated with uroculture with bacterial growth greater than or equal to 10^4 CFU/ml at a follow-up of 100 days after the procedure [19]. The last study mentioned only signs of sepsis: chills and fever at the time of the procedure with or without hypotension [(22)].

Inaccurate diagnosis can lead to inadequate treatment, resulting in irrational use of antimicrobials and, consequently, future infections with multi-resistant bacteria. This is a cause for concern, as it aggravates the clinical condition of patients with neoplasms who are already immunocompromised, both because of the tumor and the cancer treatment itself.

1.5. Is it possible to avoid a urinary tract infection related to a percutaneous nephrostomy catheter?

At the same time as there is no consensus on the definition of nephrostomy-related urinary tract infection, there is also no consensus on its prophylaxis. In order to assess it, it is necessary to take into account the formation of a biofilm of microorganisms on the catheter (perhaps this is the most important factor) and the use of antibiotics.

1.5.1. The Biofilm Question

Colonization of the nephrostomy catheter occurs as soon as it is passed into the patient [19] , leading to the development of a three-dimensional biofilm [28] , containing a high concentration of microorganisms which are under relative protection from both the immune system and antimicrobials, associated with intraluminal fouling can lead to catheter dysfunction and clinical infection, from pyelonephritis and abscesses to bacteremia and septic shock [18, (29)] .

Biofilm is therefore a reservoir of microorganisms which can perpetuate an episode of infection or even facilitate a new one [19] . Therefore, the best way to prevent infection is to use the nephrostomy catheter for as short a time as possible. However, if patients need this catheter for a long period of time, one way of mitigating catheter-related urinary tract infection would be to change the catheter after a period of use.

The time used to change the catheter varies according to expert opinion and institutional protocols, ranging from 10 weeks [30] to 3 months [3] . One study proposed a model to define the best time to change, associated with fewer complications, better patient compliance and lower costs, concluding that changes could be made every 60 days [(20)] .

In situations where urinary tract infections related to the nephrostomy catheter recur, a retrospective study suggests that the catheter should be changed up to four

(4) days after starting the appropriate antimicrobial to treat the current infection and maintain this antimicrobial for 14 days of treatment [19].

1.5.2. The question of antibiotics

Antibiotic prophylaxis in surgical procedures follows certain principles:

It is a brief administration of antibiotics before or at the beginning of an intervention used to minimize infectious complications related to diagnostic or therapeutic intervention. Even though its use is widely accepted, there are risks of side effects and the development of multidrug-resistant microorganisms [31, 32].

The potential benefit is determined by three conditions: patient-related factors (ability of the host to respond to bacterial invasion); procedure-related factors (likelihood of bacterial invasion at the surgical site) and the potential morbidity of the infection [32].

It is only recommended when the potential benefits exceed the premeditated costs and risks [32].

The antimicrobial agent used must be effective against the bacterial microorganism characteristic of the surgical site relevant to causing infectious disease, also considering the cost, convenience and safety of the antibiotic [32].

Its duration should be for the period in which bacterial invasion is facilitated and/or likely to establish an infection [32].

According to the *American Heart Association*, antimicrobials are no longer recommended in genitourinary procedures solely to prevent infective endocarditis as this is not an effective strategy. Infective endocarditis occurs as a result of random bacteremia associated with daily activities and not due to genitourinary procedures [32, 33].

However, it is only indicated against α-hemolytic streptococci in patients at high risk of developing infective endocarditis (patients with valve prostheses, previous history of infective endocarditis, congenital heart disease treated with material considered to be a foreign body or heart transplant with valvulopathy) and the use of amoxicillin or cefazolin is recommended [33, 34].

Based on these principles, antibiotic prophylaxis in urological procedures is an important and easily modifiable preventive measure to reduce postoperative infections. The decision to carry it out and the selection and dose of the antibiotic to be used can

be based on consensus, but a comprehensive assessment of the patient's specific circumstances should also be considered [32].

Thus, specifically with regard to percutaneous nephrostomy, in some situations antibiotic prophylaxis may not be carried out, as suggested by a 1991 study, in patients at low risk of sepsis related to the procedure (14% of sepsis in those patients who were not given antibiotic prophylaxis and 10% of sepsis in those who received antibiotic prophylaxis, p = 0.75). However, for patients considered to be at high risk of urinary focus sepsis after the procedure (the elderly, those with diabetes *mellitus*, those with bladder dysfunction, patients using a delayed bladder catheter, patients who had undergone previous manipulation of the urinary tract, patients with uretero-intestinal anastomosis, stones and bacteriuria) the same study found that in patients who did not receive antibiotic prophylaxis the sepsis rate was 50% and in those who received antibiotic prophylaxis the sepsis rate was 9%, p = 0.03 [22] . This study evaluated malignant and benign ureteral obstructions, mainly caused by calculi, and 12/56 (21.4%) of the patients developed signs of sepsis after percutaneous nephrostomy, but 9 of them had ureteral calculi and in 7 of these 12 patients percutaneous nephrostomy was used as an access for percutaneous nephrolithotomy [22].

It is important to note that the proportion of sepsis in this study is high due to a possible latent ureteral infection secondary to the presence of calculi, which may be an important selection bias, and thus it is not possible to compare these high sepsis rates with other clinical situations requiring percutaneous nephrostomy catheters [22, 35] . The population of patients undergoing percutaneous nephrolithotomy with latent infections secondary to calculous disease is different from populations without calculi because the infection, even if latent, in the former is prior to the procedure, and it is not possible to attribute any sign of infection to the decompression performed by percutaneous nephrostomy and then judge it as a life-threatening procedure [35].

In addition to the facts described above, the results of a 1989 study found the presence of bacteria in blood samples by collecting blood cultures before and after changing nephrostomy catheters used for long periods (not specifying the cause of ureteral obstruction) and evaluating the patients up to 24 hours after the procedures. None of them showed signs of infection and there were 11% of positive blood cultures (in 104 catheter changes) for patients who did and did not receive antibiotic prophylaxis [30].

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In addition, Maneevese *et al.* in a retrospective study showed that diabetes, ileal conduit, chronic kidney disease, ureteral catheter, previous history of urinary tract infection and neutropenia were not considered risk factors for urinary tract infection related to percutaneous nephrostomy catheter in 216 procedures, however, they do not mention whether the first procedure for urinary tract clearance or its subsequent changes were studied [36].

These older studies are the main references for drawing up some consensuses.

1.5.2.1. Urology consensus

Antibiotic prophylaxis is well established for transurethral resections of the prostate and prostate biopsies, but some systematic reviews and consensuses do not include percutaneous nephrostomy and make no mention of patients with neoplasms [31, 32].

In a review, the procedure evaluated that comes closest to percutaneous nephrostomy is percutaneous nephrolithotomy (removal of calculi, usually larger ones, directly through the obstructed kidney). Although calculous disease is benign, it can in itself be a hotbed of microorganisms, increasing the risk of urinary tract infections after percutaneous nephrolithotomy. Therefore, antibiotic prophylaxis is recommended for all procedures. Even so, when the preoperative uroculture is negative, there is little evidence to suggest a more favorable result in the prevention of urinary tract infection after percutaneous nephrolithotomy when antibiotic prophylaxis is carried out, without a clear advantage with any specific antimicrobial regimen used [31].

The second review also does not include percutaneous nephrostomy in its analysis of antibiotic prophylaxis in urological procedures, but the closest procedure evaluated is percutaneous renal surgery, and prophylaxis is indicated in all patients, but with level of evidence IIb (evidence obtained from at least one or other type of well-designed quasi-experimental study) and III (evidence obtained from well-designed non-experimental studies - comparative studies, correlation studies and case reports). Nor does it mention prophylaxis in percutaneous procedures with long-term catheters or catheter changes [32].

An important study evaluating various regions of the world on the use of antibiotics in urological procedures observed that 50% of the use of antimicrobials was for prophylaxis and that 75% of the use of all antimicrobials was empirical in nature. They conclude that there are significant differences between countries, regions and

types of hospital in the use of antibiotic prophylaxis, especially for clean procedures and the type of antibiotic used (the most common were ciprofloxacin and cephalosporins in general), which are not always consistent with evidence-based consensus [37].

More recent urological consensuses continue to recommend the use of antibiotic prophylaxis with cefazolin associated with aminoglycoside if there is manipulation of the urinary tract or implantation of prostheses in procedures considered clean-contaminated, but none of them mention percutaneous nephrostomy itself [38-41].

1.5.2.2. Interventional radiology consensus

The consensuses on antibiotic prophylaxis in procedures performed by interventional radiologists are the ones that most often mention percutaneous nephrostomy. These documents also define colonization as the presence of a microorganism without leading to a systemic inflammatory response [34, 42].

They recommend the use of antibiotic prophylaxis for all patients, except for catheter changes in non-infected cases, without obstruction and in immunocompetent patients because there is no description in the literature, but also, without guarantees, with levels of evidence ranging from historical, non-randomized or case-control studies to case series without control group, with limited data and expert opinions (grade of recommendation IIb, with level of evidence in limited data and expert opinion) [34, 42].

Brick *et al.* retrospectively evaluated 493 percutaneous nephrostomy catheter exchange procedures carried out on 126 patients, 213 procedures before a change in clinical practice and 280 procedures after this change which consisted of not carrying out antibiotic prophylaxis on patients considered to be at low risk of infection, as suggested by the consensuses described above. High risk was considered to be the presence of 2 to 5 risk factors and low risk 0 to 1 of these factors, which were type II diabetes, previous urinary tract infection, history of neoplasm or obstruction, hypertension and kidney transplantation. Using the risk stratification model used, the authors concluded that changing the prophylaxis practice used had no effect on the rate of hospital admission due to infection or on the rate of infection in outpatients, corroborating that not using antiobiotic prophylaxis for routine catheter changes in patients at low risk of infection does not increase the rate of infection [27].

1.5.2.3. Antibiotic prophylaxis for percutaneous nephrostomy in cancer patients

Few studies have evaluated this issue in the context of percutaneous nephrostomy and malignant ureteral obstruction. One of them evaluated the role of antibiotic prophylaxis in urological procedures, with percutaneous nephrostomy performed in 15.3% of patients with both benign and malignant ureteral obstruction. The patients were followed up for 30 days after the procedure, and the only event studied was the presence of fever [26] . Antibiotic prophylaxis was carried out in two ways, in the first group 30 minutes before the procedure and in the second group immediately after the procedure. Feverish complications occurred in 4.5% of both groups and in all procedures (ureteral catheters, nephrostomy and retrograde pyelography), with no statistical difference. The authors found that pyuria before the procedures and the degree of hydronephrosis were risk factors for urinary infection, and that antibiotic prophylaxis may be more beneficial in these situations [(26)] .

Another retrospective study evaluated antibiotic prophylaxis and urinary infection after the first nephrostomy catheter passages for urinary tract clearance and after catheter changes in the oncology population. Fifty-one percent of the patients studied underwent nephrostomy catheter replacement. Patients were followed up for 90 days and 19% had catheter-related pyelonephritis and 7.5% had asymptomatic bacteriuria after the first passage [3] . Half of the patients who had pyelonephritis developed the infection one month after catheter insertion. Of the patients who had their catheters changed, 4% developed pyelonephritis and 2% asymptomatic bacteriuria. The authors concluded that the rate of pyelonephritis related to nephrostomy catheter insertion is relatively high, mainly due to gram-positive germs, with previous urinary tract infection and neutropenia being the main risk factors. The authors also concluded that antibiotic prophylaxis does not prevent nephrostomy catheter-related pyelonephritis, suggesting that the main risk factor for this infection is simply the existence of tumor disease [(3)] .

A retrospective cohort carried out at this institution evaluated 180 percutaneous nephrostomies (87 first passes and 93 catheter changes) over a 3-year period. The occurrence of urinary tract infection related to the nephrostomy catheter was verified up to 7 days after the procedures, with 1.2% of urinary tract infection related to the nephrostomy catheter being identified after its first passage and 11.4% after catheter changes ($p = 0.01$) [43] . In the first passages, there was no statistically significant difference in urinary infection rates when the patient received antibiotic prophylaxis or

not (0% *versus* 1.5%, respectively; p = 0.999). In catheter changes, even without statistical significance (p = 0.146), the urinary infection rate was 21.4% in those patients who did not receive antibiotic prophylaxis; 14.8% in those who received empirical antibiotic prophylaxis and 6.4% in those who received targeted antibiotic prophylaxis (with antibiotics guided by a previously collected uroculture result) [43] . Despite the potential bias in results due to its retrospective nature, this study demonstrates a reality in clinical practice and also a possible solution both to prevent urinary infections in this population and to help rationalize the use of antibiotics.

Finally, a prospective study assessed the incidence of urinary tract infection after nephrostomy catheter changes without antibiotic prophylaxis and found that out of 126 catheter change procedures, 13.5% had infectious complications. Just over half (52.9%) required antibiotic treatment and only 1 patient was hospitalized for such treatment, but without threatening the patient's life, according to the authors [(44)] .

Consequently, there are more doubts than certainties about antibiotic prophylaxis in percutaneous nephrostomy in cancer patients.

Based on what has been said so far, two fundamental questions can be posed. Firstly: would it be necessary to carry out antibiotic prophylaxis for the first passage of the percutaneous nephrostomy catheter to prevent urinary infection related to the procedure? And secondly: can uroculture-guided antibiotic prophylaxis be superior in preventing urinary tract infection when compared to empirical antibiotic prophylaxis after percutaneous nephrostomy catheter changes guided by imaging? These are the questions that guide this research project.

2.

a) There is no consistent data in the literature to answer whether the use of antibiotic prophylaxis before nephrostomy helps prevent urinary tract infection in cancer patients;
b) There is not enough data in the literature to define the best antibiotic prophylaxis approach (prophylactic or uroculture-guided) for catheter changes in cancer patients;
c) There are no clinical trials on antibiotic prophylaxis in percutaneous nephrostomy, probably because it is difficult to perform even for ethical reasons, especially in patients with advanced cancer.
d) Nor are there any systematic reviews or meta-analyses on this subject.
e) Much of the existing literature is made up of heterogeneous studies that are not specific to the cancer population and whose results are applied in a generalized and inaccurate way, such as the irrational use of antibiotics.
f) Consensus on antibiotic prophylaxis in urological procedures does not mention percutaneous nephrostomy.

3. OBJECTIVES

3.1. Primary

- To evaluate the rate of urinary tract infection related to the percutaneous nephrostomy procedure in cancer patients, according to the use of antibiotic prophylaxis at the first catheter passage and subsequent changes, a retrospective cohort and systematic review with meta-analysis will be conducted.

3.2. Secondary

- Describe the frequency of urinary tract infection related to the percutaneous nephrostomy catheter that occurs between catheter changes (not related to the procedure, but possibly to colonization of the catheter);
- To describe and compare the results of the urocultures involved in the study, as well as their sensitivity to the antibiotics used;
- Describe the main signs and symptoms involved in urinary tract infection related to the procedure and the nephrostomy catheter;

- Assess the severity of urinary tract infections according to the type of treatment and the need for hospitalization.
- To determine the risk factors for urinary tract infection related to the passage and subsequent changes of nephrostomy catheters.
- Describe the rates of urinary infections and associated germs according to the time of nephrostomy passage, first passage or catheter change.
- Report whether these catheters were changed when the urinary tract infection occurred and on which day after the urinary tract infection was diagnosed.

4. MATERIAL AND METHODS

4.1. Study design

Hybrid design: Retrospective cohort study with systematic review and meta-analysis.

4.2. Study site

This study will be carried out in the interventional radiology department of two Pio XII Foundation hospitals (Barretos Cancer Hospital and Jales Cancer Hospital).

4.3. Factor under study

The factor under study will be antibiotic prophylaxis.

4.4. Outcome

The outcome will be urinary tract infection.

4.5. Breakdown of the methodology

This section is divided into parts I, II and III for a better understanding of the design and conduct of the study.

Part I - Retrospective Cohort Study

4.6. Inclusion criteria

- Patients with neoplasms being followed up at the Pio XII Foundation.
- Progression with malignant ureteral obstruction and need for clearance.
- Patients undergoing percutaneous nephrostomy to clear the urinary tract and for subsequent nephrostomy catheter changes.

4.7. Exclusion criteria

- Use of percutaneous nephrostomy for other procedures such as passage of a double-J catheter via the antegrade route.
- Use of percutaneous nephrostomy to treat clinical conditions other than malignant ureteral obstruction, such as stenosis secondary to Bricker's ileal conduit.
- Use of percutaneous nephrostomy to clear the urinary tract of non-neoplastic causes, such as stones or non-malignant stenosis.
- Use of antibiotics to treat urinary tract infection when performing percutaneous nephrostomy (first pass or exchange).
- Patients on suppressive antibiotic therapy.

4.8. Population

Patients of both sexes and any age with cancer being treated and followed up at Pio XII Foundation hospitals who have developed malignant ureteral obstruction requiring percutaneous nephrostomy as part of their treatment from January 2013 to June 2020 at the Jales Cancer Hospital and from January 2014 to June 2020 at the Barretos Cancer Hospital.

4.9. Sample size calculation

The retrospective cohort will be made up of 372 consecutive, non-probabilistic patients for convenience, according to data collected from the institution's hospital

system (SisOnco). These patients will be studied according to the procedures performed, divided into first catheter passage and catheter change.

In the first pass of the percutaneous nephrostomy catheter group, 372 procedures were carried out at the Barretos and Jales Cancer Hospitals. In the catheter change group, 358 procedures were carried out in the stipulated period. Totaling 730 procedures carried out at the two hospitals between January 2013 and June 2020.

4.10. Study Conduct, Measurements and Methodology

One of the main aims of this study is to assess the rates of urinary tract infection related to the percutaneous nephrostomy procedure in cancer patients. At the first catheter change, groups will be assessed according to whether or not antibiotic prophylaxis was used. At subsequent catheter changes, groups will be assessed according to the type of antibiotic prophylaxis used (uroculture-guided *versus* empirical).

Patients eligible for the study will be identified when, during follow-up at the Pio XII Foundation, there was an indication for the image-guided percutaneous nephrostomy procedure after due assessment by the urology and/or interventional radiology teams.

The medical records of patients who underwent the procedure from January 2013 to June 2020 at the Jales Cancer Hospital and from January 2014 to June 2020 at the Barretos Cancer Hospital will be retrospectively reviewed using the database provided by the institution itself (SisOnco).

4.10.1. Definitions

In order to carry out this study, it is necessary to establish some concepts, some of which are not yet standardized in the medical literature:

- **Urinary tract colonization:** occurs when there is a positive uroculture result (presence of infectious agents such as bacteria or fungi) in the absence of clinical signs suggestive of infection. In these cases, antibiotic treatment is not necessary [45].
- **Urinary tract infection:** occurs when there are signs and symptoms suggestive of local infection, such as cystitis (bladder infection or lower urinary tract infection) or pyelonephritis (kidney infection or upper urinary tract infection) associated with a positive uroculture result, requiring treatment with antibiotics [3, 19, 46].

- **Urinary tract infection related to the percutaneous nephrostomy procedure:** when the urinary tract infection occurs shortly after the procedure has been carried out, in this case, percutaneous nephrostomy (first pass or catheter changes).
- **Urinary tract infection related to the nephrostomy catheter:** when the urinary tract infection occurs at another time unrelated to the procedure and in the presence of the nephrostomy catheter and in the absence of another focus justifying the infection.

4.10.2. First pass procedure

This group will be made up of patients who have undergone percutaneous nephrostomy for urinary tract clearance and we will study whether or not antibiotic prophylaxis was recorded in the medical records to be reviewed at these hospitals.

The following laboratory tests will be considered: serum creatinine and urea levels, urine samples for tests such as urine summary (or type I urine) and uroculture with antibiogram.

The proportion of urinary tract infections that developed within 7 days of the procedure will be studied. A procedure-related urinary tract infection is considered to be any report in the medical record of clinical signs and symptoms associated with uroculture results (see definition in item 4.10.4.) and the location of the respective treatment will be documented: outpatient, inpatient or intensive care unit (ICU).

It will be documented whether there is evidence reported in medical records of urinary tract infections or the presence of bladder fistulas prior to the procedure.

4.10.3. Procedure for changing the catheter

Catheter changes take place electively approximately every 90 days after the previous procedure (first pass or previous catheter change), scheduled during outpatient follow-up. However, this change can happen earlier than planned due to situations such as catheter obstruction and migration, or even catheter-related urinary tract infection.

This group will be made up of patients undergoing percutaneous nephrostomy catheter exchange and will study the use of empirical or targeted antibiotic prophylaxis documented in medical records to be reviewed at the two hospitals.

The Jales Cancer Hospital will study targeted antibiotic prophylaxis, which consists of collecting the following laboratory tests around 7 days before the procedure

to change the nephrostomy catheter(s) to guide the antibiotic to be used for prophylaxis: serum creatinine and urea levels, urine samples for tests such as urine summary (or type I urine) and uroculture with antibiogram. If the tests are not carried out prior to the procedure or if the uroculture does not show a specific bacterial agent, the procedure will be studied according to empirical antibiotic prophylaxis.

The Hospital de Câncer de Barretos will study the empirical antibiotic prophylaxis carried out according to daily clinical practice, recorded in the medical records to be reviewed of patients undergoing percutaneous nephrostomy catheter exchange.

The proportion of urinary tract infections that developed within 7 days of the procedure will be studied. A procedure-related urinary tract infection is considered to be any report in the medical record of clinical signs and symptoms associated with uroculture results (see definition in item 4.10.4.) and the location of the respective treatment will be documented: outpatient, inpatient or intensive care unit (ICU).

It will be documented whether there is evidence reported in medical records of urinary tract infections or the presence of bladder fistulas prior to the procedure.

4.10.4. Urinary tract infection

A urinary tract infection will be considered to be the presence of clinical signs and symptoms suggestive of infection, such as fever (axillary temperature greater than 37.8ºC), chills, low back pain, pain at the wrist-percussion of the lumbar region and/or the presence of cloudy urine in the collection bag, plus a uroculture with the presence of microorganisms (no more than two) with more than 100,000 CFU/ml.

If the urinary tract infection is diagnosed 7 (seven) days after the procedure (first catheter passage or change), it will be considered a procedure-related urinary tract infection.

If a urinary tract infection is diagnosed between catheter changes, it will be considered a catheter-related urinary tract infection.

The laboratory tests to be studied will be blood count, creatinine and urea, C-reactive protein, type I urine, uroculture and antibiogram and samples of blood cultures and antibiograms collected at the time of diagnosis of the urinary tract infection.

If the participant receives treatment for a possible urinary tract infection occurred between catheter changes at another service, it will be considered an infection if there is an improvement in the symptoms reported by the participant in the medical records and the antimicrobial used for the treatment will be verified.

The antibiotic(s) used for treatment will be duly studied and registered

4.10.5. Study variables

The study variables will make up the research instrument used to collect the data (see Appendix II).

Sociodemographic and clinical variables: gender, color, age, weight, height, underlying neoplastic disease, performance status and number of organs affected by metastases. Presence of fever, low back pain, pain at the wrist-percussion of the lumbar region, pain in the hypogastrium, dysuria and polyuria and presence of cloudy urine.

Radiological data: degree of urinary tract obstruction.

Dates of diagnosis of the underlying neoplasm and diagnosis of malignant ureteral obstruction.

Laboratory data: blood count, creatinine, urea, type I urine, uroculture and antibiogram.

Antibiotics: for the prophylaxis or treatment of urinary tract infection and sensitivity of the first antibiotic used for prophylaxis and/or treatment.

Colonizing and infecting agents and their classification in terms of multidrug-resistant organisms

Period of use of the catheter(s); removal of the catheter(s); other complications, such as mobility of the catheter(s) and/or obstructions.

4.11. Data Storage Plan

Information collection will be based on a structured collection instrument (Appendix II). The information will be sought from the institution's database, corroborated by consultations with medical records and local sector records.

The data will be stored on the REDCap Platform[47] which is among the best data collection, management and storage platforms for research and multi-institutional studies. It complies with the American laws on the protection of patient data, the *Health Insurance Portability and Accountability Act* (HIPAA). In addition to secure data storage and management, research data is stored on the institution's own server.

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4.12. Statistical Analysis

The data will initially be tabulated in an electronic spreadsheet in REDCap and for the statistical analysis, only the research team's statistician will download the data into the statistical program (SPSS). The study population will be characterized using descriptive statistics, using the mean, standard deviation, minimum, maximum and quartiles for quantitative variables and frequency tables for qualitative variables.

The database will be made up of patient information and procedure information, but with a unique identifier for each patient, allowing information to be linked between them.

For the purposes of this study, nephrostomy procedures will be considered independent. The procedures will be separated into first pass and catheter changes. In the first passage, procedures with antibiotic prophylaxis and without antibiotic prophylaxis will be studied. In catheter changes, procedures with empirical antibiotic prophylaxis and with targeted antibiotic prophylaxis will be studied. The types of procedures and the other characteristics of the procedures will be associated with the occurrence of urinary tract infection using the Chi-square test or Fisher's exact test, depending on the expected values in the contingency table. The multiple analysis will be carried out using Logistic Regression with multiple variables. To this end, only the variables with a p-value of less than 0.20 in the univariate analysis will be selected for the model.

The significance level will be 5%, two-sided, for all statistical analyses, which will be carried out using the SPSS v21 program.

Part II - Systematic Review and Meta-Analysis

4.13. PICO

P (participants): cancer patients requiring a percutaneous nephrostomy procedure, at the first catheter passage and at subsequent changes.

I (intervention): Use of empirical or uroculture-guided antibiotic prophylaxis.

C (comparisons): compare patients with and without antibiotic prophylaxis and, if used, empirical or guided by uroculture.

O (outcomes): urinary tract infection.

4.14. Registration of the Research Protocol

This systematic review will be duly registered in PROSPERO (*International Prospective Register of Systematic Reviews*), since there is no record of similar research currently being carried out in this database.

4.15. Research Protocol

The protocol for the literature search will be based on the population of cancer patients requiring percutaneous nephrostomy (at the first catheter passage and subsequent changes), whose intervention will be the use of empirical or uroculture-guided antibiotic prophylaxis to compare patients with and without the use of antibiotic prophylaxis and, if used, empirical or uroculture-guided, with urinary tract infection as the outcome.

This systematic review will follow the suggestions dictated by the PRISMA recommendations (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*) [48] during its process of acquiring and synthesizing the evidence.

4.16. Database search strategy

The systematic literature search will use the PubMed (MEDLINE), Cochrane and EMBASE databases and will be carried out comprehensively and will start from May 1, 2021 until August 1, 2021.

To obtain the evidence, the literature will be researched using the terms *"nephrostomy, percutaneous"* in combination with *"antibiotic prophylaxis"*, *"urinary tract infection"*; *"ureteral obstruction"* and *"neoplasms"*. The references of the studies found in the systematic review will be evaluated in order to identify more relevant studies for this research.

4.17. Variables to be studied

From the studies found, available data will be extracted relating to the number of cancer patients undergoing percutaneous nephrostomy, type of nephrostomy (first pass, catheter exchange or undefined), neoplastic diseases that led to ureteral obstruction, whether or not antibiotic prophylaxis was taken before, during or after the procedure and the occurrence of urinary tract infection after the procedure, regardless of the date.

4.18. Inclusion Criteria

- Entire studies in English;
- No limitations on dates or type of studies (if no clinical trials are found, observational studies will be used);
- Studies showing the relationship between urinary tract infection and antibiotic prophylaxis after percutaneous nephrostomy in cancer patients, even if they contain data on benign obstructive ureteral diseases.

4.19. Exclusion Criteria

- Publication of case reports, letters, comments, conference abstracts, editorials and reviews that do not report the original data;
- Animal studies;
- Studies with duplicate populations in other studies, selecting those with more institutions or patients

4.20. Study selection Data extraction

Two researchers (J.R.Z. and R.R.) will independently review and scrutinize the studies to verify the eligibility criteria. They will begin by removing duplicate articles with a subsequent analysis of the relevance of the titles, followed by the abstracts of the articles and, finally, the articles as a whole. Disagreements will be resolved by consensus and the opinion of a third reviewer. The following flow chart summarizes the strategy that will be employed.

4.21. Organization of studies

All the studies found in the literature will be organized using EndNote X9 software to identify duplicate articles, as well as documenting them and helping with their eligibility.

4.22. Statistical analysis

The meta-analysis will be carried out using the *Comprehensive Meta-Analysis* software version 2 [49]. At this stage, we will use heterogeneity tests together with Funnel Plot and Forrest Plot graphical analyses.

4.23. Methodological quality and risk of bias assessment

As noted when this research project was conceived, no randomized studies on the subject had been found so far. Thus, to assess the quality of the studies to be researched and the risk of bias, the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions) will be used [50] . This tool provides a comprehensive and structured approach to evaluating non-randomized studies of interventions, providing a complete assessment of the risk of bias in relation to a hypothetical randomized clinical trial. It is divided into 7 domains, two pre-intervention domains (confounding bias and participant selection bias within the study), one in-intervention domain (bias in the classification of interventions) and four post-intervention domains (bias from deviations in intended interventions, bias from missing data, bias in the measurement of outcomes and bias in the selection of the reported outcome). The evaluation of each study will be divided into six stages: specify the research question in consideration of a target study; specify the outcome and result being evaluated; for the specified result, examine how confounding factors and co-interventions were addressed; answer the signaling questions for the seven domains of bias; formulate judgments of risk of bias for each of the seven domains informed by the signaling questions; and formulate an overall judgment about the risk of bias for the outcome and results being evaluated [50] . This instrument can be found in full in Appendix III.

If randomized studies are found, the tool used will be recommended by the *Agency for Healthcare Research and Quality, Cochrane* Collaboration [(51)] .

5. ETHICAL ISSUES

This project complies ethically and methodologically with the Guidelines and Regulatory Norms for Research Involving Human Beings (Resolution 466/12 of the National Health Council). It also complies with and will respect the General Data Protection Law (Law No. 13,709/2018). This research project will be submitted to the Ethics and Research Committee of the Barretos Cancer Hospital (CEP) via Plataforma Brasil.

The Ethics Committee of this institution will be asked to waive the Informed Consent Form, due to the retrospective nature of this research and the fact that it poses minimal risks to the participants, which are inherent to the accidental breach of data confidentiality, and because it involves collecting data from medical records and it is not possible to contact some selected research participants due to their death and those who are alive will not have their clinical conduct altered by the research. In addition, the researchers will be collecting data on urinary infection and its repercussions, not involving data that could compromise or alter their cancer prognosis . However, the researchers undertake to preserve the privacy of the research participants, guaranteeing that the data collected will be used solely and exclusively for the execution of the project in question, and that the information disclosed in no way identifies the research participant.

Risks:

This is a study with minimal risk, characterized by the possible breach of patient data confidentiality. Furthermore, this study will not assess oncological outcomes. However, the researchers undertake not to disclose this data and to maintain total confidentiality.

Benefits:

This study may not bring any immediate benefit to the research participant, but it may show possible future benefits for other patients.

6. PROJECT EXECUTION SCHEDULE

YEAR	2021		2022			2023			2024			2025		
MONTH		Month 5-8	Month 9-12	Month 1-4	Month 5-8	Month 9-12	Month 1-4	Month 5-8	Month 9-12	Month 1-4	Month 5-8	Month 9-12	Month 1-4		
Literature review															
Review of cases and data sheets															
Meta-analysis courses															
Data collection															
Data tabulation															
Statistics															
Evaluation results															
Participation in events															
Writing the manuscript															

7. BUDGET

A4 sheets: R$ 10.00 x 30 blocks = R$ 300.00
Photocopies: R$ 300,00
Printing ink: R$ 400,00
Computers and printers will already be available at each institution
Total approximate expenses: R$1,000.00.
Other occasional expenses will be borne by the researchers.

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9. ANNEXES

Appendix I: Classification of Outcome-Based Complications by the International Society of Interventional Radiology [21]

Minor complications:

A. does not require therapy, there are no consequences or

B. requires minimal therapy, no consequences; includes overnight admission for observation only.

Major complications:

C. require therapy, minimal hospitalization (less than 48 hours);

D. requiring increased therapy, unplanned increase in the level of care, prolonged hospitalization (longer than 48 hours);

E. have permanent adverse sequelae or

F. result in death