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Review – Endo-urology

Risk of Sepsis in Retrograde Intrarenal Surgery: A Systematic Review of the Literature

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Abstract

Context: Nowadays, urolithiasis has become a highly prevalent disease. Recent studies indicate that retrograde intrarenal surgery (RIRS) is becoming more popular among surgical treatments due to the preference of patients and providers. This minimally invasive procedure results in high stone-free rates and relatively low morbidity; however, complications resulting from infection can still occur, including acute urinary tract infection, systemic inflammatory response syndrome, and sepsis.

Objective: To identify the independent risk factors for sepsis following RIRS, as well as general risk factors that may contribute to this life-threatening complication in the pre- and intraoperative periods.

Evidence acquisition: A literature review was conducted in April 2020 using the Medline, Scopus, and Cochrane databases. We searched the references of included papers.

Evidence synthesis: We screened 2306 manuscripts and selected 13 for inclusion. The sepsis rate ranged from 0.5% to 11.1%, and the septic shock rate ranged from 0.3% to 4.6%. All selected studies mentioned risks for sepsis and/or infective complications (including sepsis), but only four of them addressed independent risks for urosepsis. These independent risk factors were stone size, high irrigation pressure, prolonged stent dwelling time (>30 d), sepsis as an indication for stent insertion, female gender, positive intraoperative bladder urine culture, longer surgical time, and diabetes mellitus.

Conclusions: RIRS is associated with a low sepsis rate, according to the latest evidence. However, given that this is a serious life-threatening complication, knowing its potential risk factors is extremely important.

Patient summary: In this report, we looked at the outcome of sepsis after planned retrograde intrarenal surgery for stone disease in patients with and without comorbidities. This information may be useful for colleagues in their daily practice.

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1. Introduction

Today, urolithiasis has become a major healthcare issue due to its increasing incidence of around 10% worldwide [1]. Its prevalence varies from 7–13% in the USA to 5–9% in Europe and 1–5% in Asia [2]. As a result of this increasing trend, it is extremely important to treat nephrolithiasis efficiently and safely.

Three commonest procedures deployed for managing upper tract stones are shockwave lithotripsy, retrograde intrarenal surgery (RIRS), and percutaneous nephrolithotomy [3], with recent studies indicating that RIRS is selectively preferred owing to patient and provider preference [4,5]. This minimally invasive procedure results in high stone-free rates and relatively low morbidity; however, complications resulting from infection can still occur. The overall complication rate after RIRS is 9–25% [6] and mostly Clavien grade I or II [7]. Nonetheless, major infectious complications can develop, those of foremost importance being acute urinary tract infection (UTI), systemic inflammatory response syndrome (SIRS), and sepsis [8]. Sepsis has classically been defined as an infection with at least two of the four SIRS criteria: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate $>90/\text{min}$, respiratory rate $>20/\text{min}$ or $\text{PaCO}_2 <32 \text{ mmHg}$, and white blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ immature band [9]. However, the validity of SIRS as a descriptor of sepsis pathobiology has been questioned [10]. Recently, the sepsis definition was updated by the “Third International Consensus Definitions for Sepsis and Septic Shock” (Sepsis 3), and it is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [10].

Sepsis caused by infection of the urogenital tract, also known as urosepsis, is the most serious complication of RIRS [11,12]. It is therefore important to identify, before the surgery, the specific risk factors for postoperative sepsis. Prior systematic reviews, meta-analyses, and retrospective studies have identified risk factors for infective complications (ICs) following RIRS, but not specifically for sepsis [13–16]. The aim of this systematic review is to identify the independent risk factors (IRFs) for sepsis following RIRS, as well as general risk factors that may contribute to this life-threatening complication in the pre- and intraoperative periods.

2. Evidence acquisition

2.1. Literature search and inclusion criteria

A literature review was conducted in April 2020 using the Medline, Scopus, and Cochrane databases, without time limits or language restriction. Separate searches were done with the following search terms: “sepsis,” “intrarenal,” “ureteroscopy,” “ureteroscopies,” “URS,” “risk factor,” and “infection.” This literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Fig. 1) [17]. Owing to the heterogeneity of study outcomes and the lack of standardized quality appraisal, a narrative synthesis of data was performed.

2.2. Data abstraction

Studies that described potential risk factors related to sepsis or infectious complications (including sepsis) in patients who underwent RIRS were included. We excluded summaries (reviews) or reports that did not include sepsis among the ICs following RIRS as well as studies that did not mention the risk factors associated with septic complications after RIRS. For discussion purposes, prior systematic reviews or meta-analyses were included.

3. Evidence synthesis

Abstracts from 2306 reports (Fig. 1) were reviewed by two researchers (A.S. and S.D.) independently. Following the removal of duplicates, 2010 studies were enrolled for abstract screening.

3.1. Results

A total of 13 studies were included in this review after abstract screening and full-text review [18–30]. The mean procedure time ranged from 25 to ≥ 210 min among the selected studies. The sepsis rate ranged from 0.5% to 11.1%, and the septic shock rate ranged from 0.3% to 4.6%. All selected studies mentioned risks for sepsis and/or ICs (including sepsis), but only four of them addressed independent risks for urosepsis. These IRFs were stone size, high irrigation pressure, prolonged stent dwelling time (>30 d), sepsis as an indication for stent insertion, female gender, positive intraoperative bladder urine culture, longer surgical time, and diabetes mellitus (DM). Results are summarized in Table 1.

3.1.1. Patient-related risk factors

3.1.1.1. Stone characteristics. In a study of 332 patients with ureteral stones between 9.2 and 10.3 mm, the stone size was found to be an IRF for sepsis following RIRS [19]. The bigger the stone, the higher the risk of sepsis. The authors did not find stone site (proximal, mid, or distal ureter) or stone side to be a risk factor for urosepsis. Zisman et al. [21] carried out a study that included 287 patients, of whom 3.1% developed sepsis in the postoperative period. Based on their findings, stone location was also found to be a risk factor for post-RIRS sepsis. Patients undergoing RIRS for kidney stones had higher sepsis rates than patients with distal or proximal ureteral stones. This difference was seen only in those patients treated with conventional antibiotic prophylactic treatment (APT; ciprofloxacin 500 mg p.o. b.i.d.); however, when two drugs were used (one dose of gentamycin 240 mg intravenously [i.v.] and ampicillin 1 g i.v. t.i.d.), this difference disappeared. In another study [22] conducted in 1493, among patients who underwent RIRS, a total of 73 suffered postoperative fever (POV; 4.9%), eight developed sepsis (0.5%), and four developed septic shock (0.3%). The authors found that patients with infection stones (ie, struvite, carbonate apatite, and ammonium urate) were more likely to suffer postoperative ICs and concluded that infection stones were an IRF of post-RIRS fever.

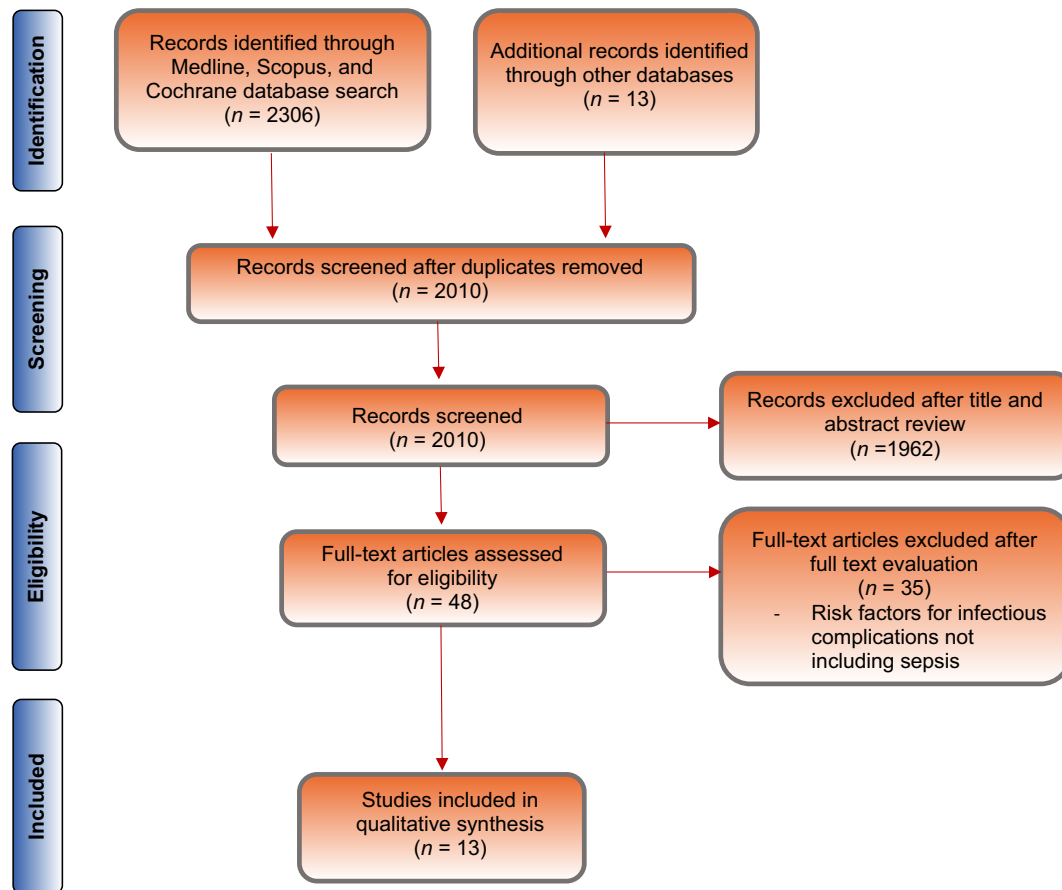


Fig. 1 – Flowchart of the literature review.

3.1.1.2. *Gender, age, and comorbidities.* In three studies [20,22,30], female gender was found to be a risk factor for sepsis, but only one study [24] concluded that female gender was an IRF for sepsis after RIRS.

Another study found that younger patients had more ICs (34.8 vs 44.7 yr old, $p < 0.001$), suggesting that patients under the age of 40 yr are more likely to suffer from this event [28]. The authors also concluded that the presence of renal abnormalities was significantly more common in patients with infectious complications (12.3% vs 35.5%, $p < 0.001$).

Furthermore, among patient comorbidities, we found that DM was considered an IRF for sepsis [26].

3.1.1.3. *Sepsis and antibiotic therapy prior to RIRS.* Díaz Pérez et al. [30] performed RIRS on 246 patients; 18 of these patients (7.3%) developed urosepsis. They found that patients who experienced the clinical onset of lithiasis in the form of urinary sepsis were more likely to develop sepsis after RIRS. Additionally, they also mentioned that other risk factors for sepsis were a history of antibiotic therapy and double J dwelling during the nephritic colic. Moreover, Nevo et al. [24] also found that patients who undergo ureteroscopy after ureteric stent insertion have a higher risk of postoperative sepsis. They concluded that prolonged stent dwelling time (>30 d) and sepsis as indications for stent insertion were IRFs for sepsis.

Another study [25], which included 345 elective RIRS patients, had a sepsis rate of 4.3%. According to the authors, patients with prior endoscopic procedures and especially those recently treated for a urinary infection should be monitored carefully after RIRS for signs of sepsis.

3.1.1.4. *Urine culture.* The presence of a positive preoperative urine culture was associated with postoperative sepsis [20,23,29,30] and infectious complications in general [21,22]. Blackmur et al. [23] emphasized on the midstream sample of urine, which they found to be significantly associated with postoperative urosepsis in not preselected patients. Bai et al. [29] concluded that positive preoperative multidrug resistance (MDR) urine culture was significantly associated with urosepsis after RIRS. One of the largest cohort studies that examined five different urinary tract cultures and the relationship between these cultures and sepsis after RIRS found that the positive intraoperative bladder and kidney urine cultures as well as the stent-end culture were highly related to sepsis [20]. Moreover, a positive intraoperative bladder urine culture was an IRF for postoperative sepsis.

3.1.2. *Surgery-related risk factors*

3.1.2.1. *Antibiotic prophylaxis.* One study focused only on the APT for RIRS. In their study, the authors compared the conventional APT, ciprofloxacin 500 mg p.o. b.i.d, with a new double-drug APT, gentamycin 240 mg i.v., and ampi-

Table 1 – Study, sepsis rate, and identified risk factors for urosepsis among included studies

Study	N	Male: female ratio	Mean age (yr)	Irrigation during URS	Mean operative time (min)	Type of infection (%)	Identified risk factors for urosepsis
Sugihara et al. (2013) [18], RC	12 372	7918:4454	≤59–≥80	NA	≤59–≥210	Sepsis ^a Septic shock ^a	Longer surgical time Lower hospital volume
Hu et al., 2016 [19], RCC	332	185:147	43	Gravity at 80, 120, and 160 mmHg	NA	Sepsis: 25 (7.5) Severe sepsis: 24 (7.2) Septic shock: 10 (3)	Stone size ^b High irrigation pressure ^b
Blackmur et al. (2016) [23], PC	462	NA	[55]	NA	NA	Sepsis: 34 (7.4)	Preop. urine culture (+)
Nevo et al. (2017) [24], PC	1256	870:386	[57]	Pressurized irrigation: 40 mmHg ^c 90 mmHg ^d	[51]	Sepsis: 36 (2.8)	Prolonged stent dwelling time (>30 d) ^b Sepsis as an indication for stent insertion ^b Female gender ^b
Bloom et al. (2017) [25], RC	345	173:172	50	NA	84	Sepsis: 15 (4.3)	UTI treatment within the last month Prior endoscopic procedures Multiple comorbidities Longer surgical time
Xu et al. (2018) [26], RC	305	144:161	51	Gravity at 60, 80, and 100 mmHg	25	Sepsis: 31 (10.2) Septic shock: 14 (4.6)	High irrigation pressure ^b Longer surgical time ^b DM ^b
Ogreden et al. (2018) [27], RC	72	56:16	44	NA	NA	Fever: 38 (52.8) UTI: 27 (37.5) Sepsis: 8 (11.1)	Stent insertion following URS (ureteral stones) in patients with PFS
Ozgor et al. (2019) [28], PC	494	273:221	35	Gravity (<74 mmHg)	65	Fever ^a Sepsis ^a Septic shock ^a	Longer surgical time (>60 min) Renal abnormality Age (<40 yr)
Bai et al. (2019) [29], RC	1421	880:541	59	Manual irrigation pump	[62]	Sepsis: 12 (0.8)	Preop. MDR urine culture (+) Longer surgical time
Díaz Pérez et al. (2019) [30], RC	246	155:91	52	Manual irrigation pump	68	Sepsis: 18 (7.3)	Female gender Preop. urine culture (+) History of urosepsis Prior antibiotic therapy Preop. stent insertion Residual lithiasis after URS
Wood et al. (2019) [20], PC	281	193:88	60	NA	NA	Sepsis: 16 (5.7)	Intraop. bladder urine culture (+) ^b Female gender Steroid use Preop. urine culture (+) Stent-end culture (+) Kidney urine culture (+)
Zisman et al. (2020) [21], RC	287	211:76	51	NA	NA	Fever: 13 (4.5) Sepsis: 9 (3.1)	Preop. urine culture (+) Stone location (upper and distal ureteral stone) Conventional APT (oral ciprofloxacin)
Peng et al. (2020) [22], RC	1493	913:580	49	Syringe manual irrigation	30	Fever: 75 (4.9) Sepsis: 8 (0.5) Septic shock: 4 (0.3)	Female gender Preop. urine culture (+) Infection stone Postop. neutrophil ratio >75%

APT = antibiotic prophylactic treatment; DM = diabetes mellitus; Intraop. = intraoperative; MDR = multidrug resistance; N = sample size; NA = not available; PC = prospective cohort; PFS = perirenal fat stranding; Postop. = postoperative; Preop. = preoperative; RC = retrospective cohort; RCC = retrospective case-control; URS = ureteroscopy; UTI = urinary tract infection.

Values in [] indicate medians.

^a % Not specified.

^b Independent risk factors of urosepsis.

^c Semirigid ureteroscopy.

^d Flexible ureteroscopy.

collin 1g i.v. t.i.d. [21]. Based on the analysis of 287 patients, the sepsis incidence was 3.1%, and it was higher in patients who used the conventional APT (7.5% vs 0.5%).

3.1.2.2. *Surgical time.* Sugihara et al. [18] showed a positive linear relationship between operative duration and severe adverse events (AEs), including sepsis. Similar results

were reported in other studies, where longer operative time was also a risk factor for developing sepsis after RIRS [25,26,28,29]. Moreover, Xu et al. [26] found that operation time was an IRF for post-RIRS sepsis.

3.1.2.3. Irrigation pressure. High irrigation pressure was found to be an IRF for urosepsis in two different studies.

The first study, by Hu et al. [19], used irrigation pressure of 80, 120, and 160 mmHg, and the second study, by Xu et al. [26], used irrigation pressure of 60, 80, and 100 mmHg. Both studies concluded that sepsis rates after RIRS increased proportionately with higher irrigation pressure.

3.1.2.4. Stenting. Ogreden et al. [27] evaluated the impact of stenting after RIRS in patients with ureteral stones and perirenal fat stranding, and concluded that double J stent insertion following RIRS increased the risk of postoperative infections in these patients.

3.1.2.5. Lower hospital volume. Sugihara et al. [18] hypothesized that hospital volume was inversely associated with the occurrence of severe AEs in RIRS, as well as extracorporeal shockwave lithotripsy and percutaneous nephrolithotomy. Compared with low-volume hospitals (≤ 15 RIRS procedures per year), medium-volume ones (16–38 RIRS procedures per year) reported a 20% reduction in severe AEs, including sepsis. Additionally, high-volume hospitals (≥ 39 RIRS procedures per year) achieved an additional 20% reduction in severe AEs.

3.2. Discussion

Nowadays, RIRS is generally considered an outpatient procedure due to its safety [31]. However, even if rare, bleeding and infectious complications may occur [32]. Among infectious complications, POF is most common [33], and unplanned hospitalization is primarily caused by POF or SIRS [34]. POF/SIRS must be recognized and managed as soon as possible to avoid progression to sepsis, which has a mortality rate of 28.3–41.1% [12].

Study definitions of sepsis were heterogeneous. Most of the studies included in this review [20,21,23,24,27–30] used the initial definition of sepsis that claimed that sepsis resulted from a host's SIRS to infection [9]. Two studies [19,26] used the most recent definition from Sepsis 3 [10], whereas only one study [22] based their sepsis diagnosis on two or more criteria of the quick sepsis-related organ failure assessment: systolic blood pressure < 100 mmHg, highest respiratory rate > 22 bpm, and lowest Glasgow coma score < 15 . Based on a recent systematic review and meta-analysis of urosepsis following RIRS, rates of postoperative sepsis ranged from 0.2% to 17.8% [35], which is in line with the sepsis rate we obtained in our study, which ranged from 0.5% to 11.1%. In spite of its low rate, urosepsis carries risks of extended hospitalization, unplanned intensive care admission, and death [36]. Identifying early predictors of sepsis after RIRS is imperative in determining patients' risk stratification as well as the intraoperative management.

Across the published literature regarding factors associated with post-RIRS sepsis, there is a lack of consensus. The previous studies either reported general risk factors

for IC [14,15] or included studies where sepsis was mentioned as a potential complication, without specifying the potential risk factors related to sepsis [13,32,37]. In our study, we found that female gender, DM, stone size, sepsis as an indication for stent insertion, prolonged stent dwelling time (> 30 d) before RIRS, high irrigation pressure, longer surgical time, and positive intraoperative bladder urine culture were IRFs for sepsis after RIRS.

It has previously been published that women experience higher sepsis rate after ureteroscopy than men [7,15,37]. The shorter urethral length of women could explain this, as it increases the possibility of colonization by perineal and rectal bacteria [15,38]. Martov et al. [39] confirmed that female gender was a specific risk factor for infectious complications after RIRS. In contrast, other reports state that female gender is irrelevant in the occurrence of SIRS or sepsis [11,40]. In our study, female gender was constantly found as a risk factor for sepsis [19,21,23,29]. Moreover, patients with comorbidities were more likely to develop fever or UTI following RIRS [39]. In terms of comorbidities related to urosepsis, the results were not consistent. While some authors showed that comorbidities such as ischemic heart disease, chronic kidney disease (CKD), immunodeficiency, and chronic indwelling urinary catheter were not associated with a higher urosepsis risk [23,30], others found that steroid use and CKD were significant risk factors for urosepsis [20]. However, among comorbidities, DM has been highlighted as a potentially significant risk factor for postoperative infections [23,41] and also as an IRF for urosepsis after RIRS [42]. This result was consistent with our study, which showed that DM was also an IRF for urosepsis [26]. Concerning anomalous kidneys, there was only one study that included patients with kidney malformations (ie, horseshoe kidney) [28]. The authors found that anomalous kidney was a predictive factor of infectious complications following RIRS. Recently, a high-volume international multicenter study, including 19 high-volume centers, concluded that RIRS in patients with anomalous kidneys is safe and effective with a high single-stage stone-free rate and low complication rate [43].

Another risk factor was the stone size. The size of the stone was cited as an IRF for sepsis following RIRS; the bigger the stone, the greater the risk for urosepsis [19]. Additionally, longer operative time was also associated with a higher sepsis risk. This is supported by different authors [24,44] who also found that longer operative time was related to severe AEs after RIRS, such as sepsis. Ozgor et al. [28] determined that surgeries lasting over 1 h doubled the risk of developing infectious complications. Xu et al. [26] found operative time to be an IRF for sepsis; hence, it is extremely important to control this factor. Furthermore, a long RIRS duration may also cause persistently high intrarenal pressure. High irrigation pressure can lead to pyelorenal backflow, which occurs when contents of the renal pelvis and calyceal system permeate beyond their normal limits, to the peripelvic sinus tissue (pyelosinus backflow), renal vein (pyelovenous backflow), collecting ducts and tubules (pyelotubular backflow), or renal interstitium (pyelointerstitial backflow) [45]. This condition occurs at pressure as low as 13.6–27.2 cmH₂O, and at 40.8–68

cmH₂O it becomes evident [45,46]. All this may also increase the risk of infection after surgery [47] due to the entrance of pathogens and endotoxins into the blood stream [47,48]. Xu et al. [26] found that patients who underwent RIRS with high irrigation pressure had a significantly higher risk of postoperative urosepsis, and classified this item as an IRF for sepsis following RIRS. Hence, in clinical practice, RIRS should be performed under low irrigation pressure (below 40 cmH₂O or 30 mmHg). It has been proposed that small-sized ureteral access sheaths (UASs) can provide low intrarenal pressure with good irrigation inflow and outflow when using a small-sized flexible ureteroscope [49]. Nonetheless, UASs were not used in either of the two studies [19,26] that focused on irrigation pressure and urosepsis. One study only mentioned that UASs did not reduce the risk of urosepsis after RIRS [23].

Multiple studies have found pyuria or positive preoperative urine cultures to be associated with ICs after RIRS [34]. Kazan et al. [50] performed a study about the role of preoperative urinalysis in predicting postoperative infection after RIRS in patients with and without a history of UTI, and the results showed that postoperative infection developed more frequently in patients who have had a history of UTI. Moreover, positive preoperative MDR urine culture has highly been associated with urosepsis after RIRS, despite appropriate preoperative antibiotic therapy [29]. This is of particular importance because the prevalence of MDR pathogens in patients with UTI is gradually increasing worldwide, perhaps due to the inappropriate antibiotic use and unnecessary anti-infective treatments [51]. The presence of positive preoperative urine cultures is associated with intraoperative stent colonization, but not with intraoperative urine colonization [20]. This brings us to another important urine culture highly associated with infectious complications, the intraoperative bladder urine culture. This urine culture was found to be an IRF for sepsis after RIRS. A nonsterile bladder urine culture was the strongest predictor of postoperative urosepsis, as it was 11 times more likely to cause the disease than a sterile culture [20].

There is still some debate, however, as to whether previous sepsis and emergency drainage pose a risk for developing sepsis after RIRS. Nevo et al. [24] found that sepsis as an indication for stent insertion and prolonged stent dwelling time before RIRS were IRFs for urosepsis. Stent dwelling time of >30 d was associated with a five-fold higher risk of urosepsis compared with dwelling time of ≤30 d. Similar results were found by Moses et al. [31], who demonstrated that indwelling ureteric stents before the procedure or longer operating time was associated with a higher rate of infection-related hospital readmissions. According to a recent prospective study, elective RIRS achieved excellent outcomes in patients who previously presented with obstructing calculi and sepsis needing emergency decompression [52]. This latest study included only patients who underwent prior sepsis; meanwhile, the previous ones [24,31] included patients who underwent elective RIRS in general. It would be important to determine the safety of stent dwell time in this high-risk group [52]. On the contrary, it has also been proposed that patients with positive preoperative midstream sample of urine and no stent

in situ are more likely to be obstructed and have stagnant urine, which could become infected and lead to urosepsis. It may therefore be suggested that the drainage provided by the stent outweighs the risk of foreign body and biofilm formation in these cases.

In addition, only one study included in this review evaluated a potential postoperative event that could be related to sepsis, the presence of residual fragments. According to this report [30], the presence of residual fragments on image examination (c-ray, ultrasound, or noncontrast uroscanner) in the 3 mo after surgery was significantly associated with the development of urinary sepsis after RIRS. Further studies need to be conducted to confirm this statement.

3.3. Limitations

The study is not without limitations. First, most of the studies included in this analysis were retrospective, except for two. Second, it was not possible to evaluate whether a publication bias was present. Third, indications for preoperative stent placement and average dwell time were rarely reported, limiting our ability to analyze these data in a more thorough manner. Finally, important information such as the use of UASs, laser settings, and surgeon experience is missing in most publications.

4. Conclusions

RIRS is associated with a low sepsis rate, according to the latest evidence. However, given that this is a serious life-threatening complication, knowing its potential risk factors is extremely important. Female gender, DM, stone size, sepsis as an indication for stent insertion, prolonged stent dwelling time (>30 d) before RIRS, high irrigation pressure, longer surgical time, and positive intraoperative bladder urine culture were IRFs for sepsis after RIRS. This information may be useful for colleagues in their daily practice.

Author contributions: Mariela Corrales had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Corrales, Traxer.

Acquisition of data: Sierra, Doizi.

Analysis and interpretation of data: Corrales, Doizi, Sierra.

Drafting of the manuscript: Corrales, Traxer.

Critical revision of the manuscript for important intellectual content: Traxer, Doizi.

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Other: None.

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