World Journal of Urology (2024) 42:189
https://doi.org/10.1007/s00345-024-04816-6

ORIGINAL ARTICLE

International Alliance of Urolithiasis (IAU) guideline on staghorn calculi management

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Received: 2 August 2023 / Accepted: 16 January 2024

Abstract

Background The stone burden based management strategy reported in the guidelines published by different associations is well known for a long time. Staghorn calculi, representing the largest burden and most complex stones, is one of the most challenging cases to practicing urologists in clinical practice. The International Alliance of Urolithiasis (IAU) has released a series of guidelines on the management of urolithiasis.

Purpose To develop a series of recommendations for the contemporary management management of staghorn calculi and to provide a clinical framework for urologists treating patients with these complex stones.

Methods A comprehensive literature search for articles published in English between 01/01/1976 and 31/12/2022 in the PubMed, OVID, Embase and Medline database is performed. A series of recommendations are developed and individually graded following the review of literature and panel discussion.

Results The definition, pathogenesis, pathophysiology, preoperative evaluation, intraoperative treatment strategies and procedural advice, early postoperative management, follow up and prevention of stone recurrence are summarized in the present document.

Conclusion A series of recommendations regarding the management of staghorn calculi, along with related commentary and supporting documentation offered in the present guideline is intended to provide a clinical framework for the practicing urologists in the management of staghorn calculi.

Keywords Guideline · Urolithiasis · Staghorn calculi · Kidney stones · Treatment

Introduction

Aims and scope

Urolithiasis is one of the most common benign urological conditions in general urological practice, its management involves a variety of medical and surgical treatments [1]. Guidelines are generally advisable to promote evidence-based management of certain pathologies and reduce the existing variability in clinical practice. The stone burden-based management strategy reported in the guidelines published by different associations is well known for a long time [2, 3]. Staghorn calculi, representing the largest burden and most complex stones, is one of the most challenging cases to practicing urologists in clinical practice [4].

The International Alliance of Urolithiasis (IAU) has aimed to develop a series of recommendations for management of urinary tract stones, primarily involving the surgical, medical, and perioperative management [5, 6]. The present document is the fifth guideline in the IAU-guideline series, addressing the management of staghorn calculi and with the goal to provide a clinical framework for urologists treating patients with these complex stones.

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Published online: 25 March 2024

IAU guideline panel on staghorn calculi management

The IAU guideline panel on staghorn calculi management comprises a group of international experts in urolithiasis, with expertise in surgical management and medical treatment of urolithiasis. A total of 36 experts are invited to participate in the IAU panel on staghorn calculi. No conflict of interest is declared.

Materials and methods

Data identification

A comprehensive literature search for articles published in English between 01/01/1976 and 31/12/2022 in the PubMed, OVID, Embase and Medline database is performed. Key terms of "staghorn calculi", “staghorn calculus”, “staghorn stone”, “staghorn stones” are selected. Candidate articles are screened after abstract and/or full-text reading, further review and summarization is required (Fig. 1).

Grade of recommendations and level of evidence

A series of recommendations are developed based on the evidence obtained and the balance between desirable and undesirable consequences of alternative management strategies [3]. Recommendations strength is graded (GR) using a modified GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology, but the range from A to C representing high-, moderate-, and low- strength, respectively [7, 8]. Based on the certainty of the results (precision, consistency, heterogeneity, and other statistical or study related factors), the level of evidence (LE) from the references is graded. Two rounds modified Delphi survey and an additional group meeting are required to formulate the final draft of the present guideline.

Guideline

Definition of the staghorn calculi

- Staghorn calculi are large branched stones that in continuous integrity fill renal pelvis and at least two of the calyces (GR: A, LE: 4).

Staghorn calculi are large branched stones that in continuous integrity fill the renal pelvis and branch into two or more of the calyces [9, 10]. They are further classified as complete or partial based on the degree of involvement of the collecting system. Partial staghorn calculi branch into at least two calyces, while complete staghorn calculi involve most

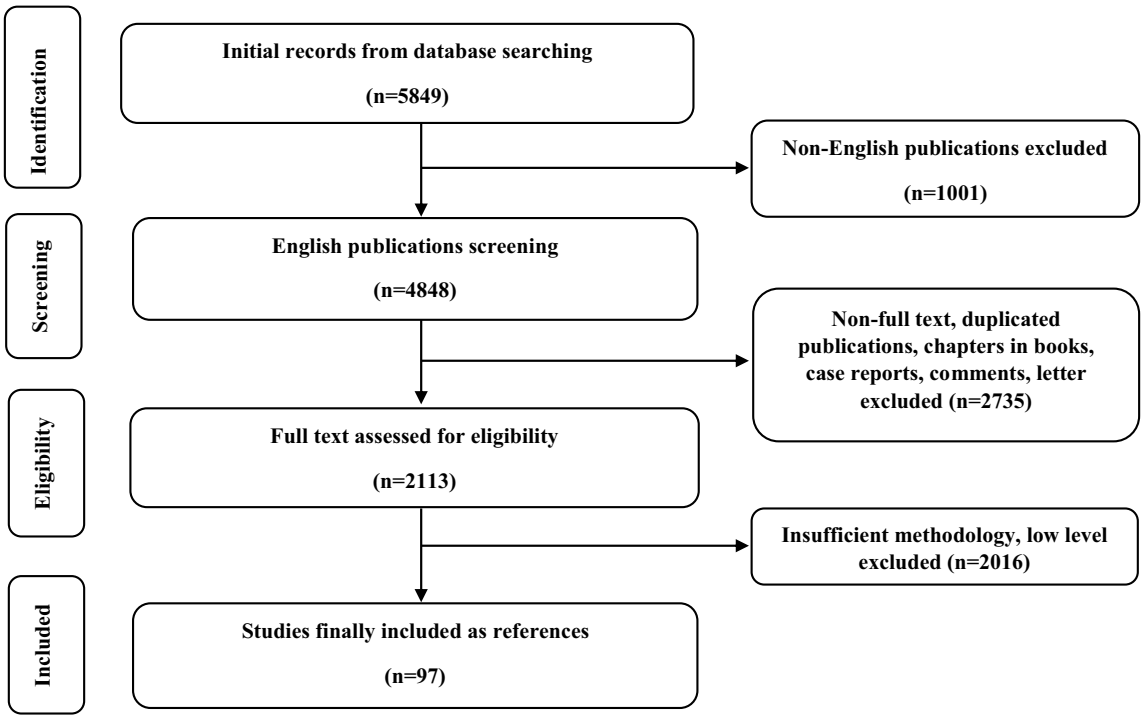

Fig. 1 PRISMA diagram for the guideline references screening

(at least 80%) calyces. Regardless of complete or partial, staghorn calculi are in continuous integrity, in contrast to multiple location stones without any demonstrated continuous integrity [11].

Pathogenesis of staghorn calculi formation

- Obstruction and urinary tract infection (UTI) with urease-producing bacteria promote formation of infection staghorn calculi. (GR: A, LE:4)

Historically, most staghorn calculi are reported as struvite with or without calcium carbonate apatite, occasionally are cystine or uric acid [4]. However, recent studies suggest that metabolic stones of calcium oxalate and calcium phosphate comprise an increasing proportion of staghorn calculi [12].

Infection stones (struvite with or without carbonate apatite) form as a result of recurrent urinary tract infection (UTI) with urease-producing bacteria [13]. Urease hydrolyzes urea, producing ammonia and carbon dioxide, which is furtherly hydrolyzed to produce bicarbonate and ammonium. In the resulting highly alkaline urine, ammonium combines with cations to form inorganic salts and sediment finally into branched staghorn calculi [14]. Bacteria also metabolize citrate in urine, reducing urinary inhibitory activity against calcium oxalate and calcium phosphate.

Although, to date, there are no clear explanations for the shift in staghorn calculi composition from infection stones to metabolic stones, it has been hypothesized to be due to dietary and lifestyle changes accompanying improved living standards [15]. Insulin resistance and metabolic syndrome as a result of obesity have been implicated in the formation of uric acid and calcium oxalate stones [16–18]. Other predisposing factors for staghorn stone formation include obstruction, functional and/or anatomical abnormalities (such as horseshoe kidney, neurogenic bladder, urinary diversions etc.) and long-term indwelling catheters [19].

Pathophysiology of staghorn calculi

- Obstruction and infection may contribute to gradual loss of renal function in patients with staghorn calculi. The objective of treatment is to achieve complete stone removal, thereby eradicating bacteria and preventing recurrent UTIs and further loss of renal function. (GR: A, LE:3)

Staghorn calculi occupy the renal pelvis and most calyces, thus to obstruct the collecting system resulting in hydronephrosis and secondary UTI [10, 20]. Recurrent UTI with urease-producing bacteria promote the formation of infection stones [21]. On the other hand, struvite-apatite dust formation facilitates the bacterial colonization which further serves as a source of repeated infections [22]. Obstruction, infection, and stones promote each other, therefore making the situation worse.

Untreated, persistent obstruction, and/or recurrent UTIs are likely to impair renal function in patients with staghorn calculi [23]. Improved knowledge of the natural history of staghorn calculi has led to significant changes in the rational management strategies of these stones [24]. The main objectives are complete eradication of stone and bacteria, with the aim to preserve renal function. Thus, a surgical management strategy is the mainstay of staghorn calculi management [20, 23].

Preoperative evaluation

- In addition to preoperative routine blood analysis, coagulation functions and serum electrolyte/creatinine levels, routine microscopic urinalysis with midstream urine (MSU) culture test is essential (GR: A, LE: 3).
- Non-contrast computer tomography (NCCT) is mandatory to outline stone characteristics before surgical intervention in patients with staghorn calculi (GR: A, LE: 3).
- 99mTc-DTPA or MAG3 renal dynamic imaging is recommended to evaluate split renal function, if there is suspicion of ipsilateral renal dysfunction (GR: B, LE: 3).

Safe and successful percutaneous nephrolithotomy (PCNL) in patients with staghorn calculi requires adequate preoperative evaluation and optimal control of surgical risk factors. Available evidence-based data indicate that positive urine cultures, nitrate-positive urinalysis, and/or pyuria are independent risk factors for urosepsis or other postoperative infections following PCNL [25–27]. A simple dipstick urinalysis and microscopic analysis are recommended as a clinical screening test because it is inexpensive and quick, but only a urine culture can guide appropriate perioperative antibiotic administration. PCNL is considered contraindicated in patients with coagulation disorders due to significant bleeding risk [28, 29]. A careful medical history aimed at eliciting history of any abnormal bleeding or coagulation dysfunction, including anticoagulation drugs, is essential. Preoperative complete blood count assesses hemoglobin status and potential systemic inflammation [30]. Assessment of electrolyte and renal function can facilitate selection of appropriate perioperative antibiotics and other medications, as well as treatment strategies.

NCCT defines the anatomy of the kidney with respect to the intestine, liver, spleen, and pleura and intrarenal anatomy, and it also delineates stone characteristics, such as attenuation coefficient (Hounsfield unit) as a surrogate for stone density, stone burden, stone location, and stone

distribution; thus, it may provide important information for preoperative surgical planning [31, 32]. In selected complex cases, CT urography and 3D-CT reconstruction may provide greater detail to facilitate access planning [33, 34]. Guy's stone score, S.T.O.N.E. nephrolithometry, the CROES nomogram, and S-ReSC are contemporary scoring systems developed to assess case complexity, postoperative results, and complications [35–37].

99mTc-DTPA or MAG3 renal dynamic imaging is recommended to evaluate split renal function, if there are signs of ipsilateral renal functional loss [38]. Preoperative evaluation of baseline renal function is crucial to outline it in the preoperative informed consent and postoperative follow-up of renal functional status [39–41]. The diagnosis of a poorly functioning ipsilateral kidney may prompt other rational therapeutic options, such as observation or nephrectomy. In cases of moderate/severe hydronephrosis associated with staghorn calculi, dynamic renal scintigraphy can exclude or confirm obstructive curve and determine if a UPJ obstruction should also be treated, or a narrowing is a consequence of stone presence.

Antibiotics and antithrombotic therapy

- A single dose of antibiotic is sufficient for prophylaxis prior to PCNL in patients with a negative urine culture (GR: A, LE: 1).
- ≥ 7 days of culture-specific antibiotics are recommended in patients with a preoperative positive urine culture (GR: A, LE: 1).
- Stone culture is recommended to guide postoperative antibiotic treatment and to prevent further recurrent UTI and struvite stone recurrence in follow-up (GR: A, LE: 3).
- The temporary discontinuation of anticoagulation or antiplatelet therapy, and/or bridging should be discussed with the cardiologist or other specialists (GR: A, LE: 1).

Preoperative prophylaxis with a single-dose antibiotic is sufficient in patients with negative urine culture, regardless of urinalysis [42, 43]. Preoperative treatment with antibiotics according to the bacterial sensitivity pattern should be administered for ≥ 7 days in patients with positive urine cultures [44, 45]. Multi-drug resistant is a significant risk factor for postoperative infectious complications despite appropriate preoperative antibiotics [46].

Intraoperative stone culture seems to be more sensitive and reliable than preoperative midstream urine culture [47, 48]. It is recommended especially in patients with preoperative negative urine culture but potential intraoperative infection signs. The postoperative antibiotic treatment strategy should be tailored according to stone culture [42]. To prevent further recurrence of UTI and struvite stones, a stone culture is also recommended for antibiotics selection [49]. Therefore, stone culture should be routinely obtained in patients with staghorn calculi.

Since PCNL is a procedure with high risk of bleeding, discontinuation of antithrombotic therapy is required prior to PCNL [5]. The temporary discontinuation of anticoagulation or antiplatelet therapy, and/or bridging should be discussed with the cardiologist or other specialists. A detailed description of the antithrombotic therapy management strategy is presented in IAU-PCNL guideline [5].

Management of staghorn calculi

Conservative observation

- Conservative management of staghorn calculi should be offered only for patients who are considered not suitable for surgical intervention (GR: B, LE: 3).

Patients with staghorn calculi have a high mortality rate (28%) and high risk of renal failure (36%) over a 10-year period if treated conservatively [23, 24]. Conservative management of staghorn calculi should be offered only for patients who are considered not suitable for surgical intervention. A few studies have concluded that conservative management combined with appropriate monitoring can be safe in asymptomatic patients who are unwilling to undergo surgery or have significant surgical risk factors. However, patients with pain, hematuria, or repeated UTIs should be considered for surgical intervention when the benefits outweigh the risks [50, 51].

Percutaneous nephrolithotomy (PCNL)

- PCNL is the gold standard first-line treatment for the majority of staghorn calculi. (GR: A, LE: 1)
- Endoscopic combined intrarenal surgery (ECIRS) is an alternative treatment option to multi-tract PCNL in the management of staghorn calculi. It may reduce the need for multiple tracts, potentially resulting in less tract-related complications, and it also may improve SFR (GR: A, LE: 2).

Most RCTs demonstrated superiority of PCNL over RIRS, SWL or open stone surgery in the management of staghorn calculi [52, 53]. PCNL remains the gold standard treatment for staghorn calculi based on high SFRs and relatively low complication rates. Mini-PCNL is also an acceptable option for treating some patients with staghorn calculi. When compared to standard PCNL, mini-PCNL achieves non-inferior SFRs, but with less bleeding, less postoperative pain, and shorter hospital stay [54]. However, selection of

patients appropriate for mini-PCNL versus standard PCNL has not yet been completely defined.

Often staghorn calculi require multiple tracts and sessions of PCNL to achieve a satisfactory result; cautious manipulation is required to reduce risk of complications [55]. Fluoroscopy guidance or fluoroscopy combined with ultrasound guidance may be more effective in multi-tracts PCNL to get a high SFR and well controlled bleeding risk [56]. Ultrasonic, pneumatic, and dual-combination lithotriptors, as well as high-power Ho:YAG and thulium fiber lasers are all effective intracorporeal lithotripsy options for disintegration of staghorn calculi during PCNL; however, laser lithotripsy is more time consuming [57].

ECIRS may reduce the need for multiple tracts in PCNL, resulting in fewer tract-related complications and shorter hospital stay [58, 59], although low lithotripsy efficiency and extra cost from flexible ureteroscopy/nephroscopy in ECIRS are controversial. The optimal patient selection criteria for ECIRS versus PCNL have not yet been definitely established.

Retrograde intrarenal surgery(RIRS)

- RIRS monotherapy is not recommended as the first-line treatment for most staghorn calculi, although it may be considered in selected patients (GR: A, LE: 3).

Although RIRS in management of stones larger than 2 cm is feasible [60, 61], multiple session RIRS are often required for staghorn calculi, and therefore RIRS is not considered first-line choice for staghorn calculi. In patients with contraindications for PCNL, or who refuse PCNL, RIRS is an acceptable alternative modality.

Several strategies can be used to optimize stone fragmentation and shorten operation time in RIRS treating staghorn calculi. Advances in the field of RIRS, such as large caliber ureteral access sheath (UAS), UAS with suction, steerable UASs, high-power lasers, and lastly the introduction of thulium fiber laser can accelerate stone removal in RIRS [62–64]. Disposable flexible ureteroscopes may eliminate flexible ureteroscope damage in a long-lasting RIRS procedure [65].

Robotic/laparoscopic/open surgery

- Robotic/laparoscopic/open surgery may be considered in patients undergoing urinary tract reconstructive surgery or failed in PCNL/RIRS for stone removal. (GR: B, LE:3)

With the high safety and effectiveness of minimally invasive procedures, open surgery is no longer considered as the first-line treatment option for the management of staghorn calculi [53]. However, in patients with complex anatomy, in which PCNL and RIRS seem very difficult or have failed, open stone removal can be considered [66]. Robot-assisted or laparoscopic procedures have been adapted from open surgery in a similar fashion. These approaches remain second- or third-line therapies when compared to less invasive endourological techniques, except in cases where stone removal is done in combination with reconstructive surgery (i.e., pyeloplasty) [67].

Shockwave lithotripsy (SWL)

- SWL monotherapy is not recommended for the management of staghorn calculi in adult patients (GR: A, LE: 1).
- SWL monotherapy may be considered as the first-line therapy in children with staghorn calculi in non-dilated collecting systems (GR: A, LE: 2).

SFR following SWL monotherapy for staghorn calculi are low, ranging from 18 to 67% and require secondary procedures in as many as 50% of patients [52]. Furthermore, infectious and obstructive complications following SWL monotherapy of staghorn calculi, including sepsis, obstructive nephropathy from steinstrasse, renal colic, and perinephric/subcapsular hematoma, are higher than for smaller volume stones [68–70]. Thus, SWL monotherapy is generally not considered as the first-line treatment for staghorn calculi.

Staghorn calculi in children generally reflect smaller stone burden, greater stone fragility, lower impedance to shock waves, and shorter skin-to-stone distance, which may facilitate better shock-wave transmission, and therefore improved stone fragmentation and clearance compared to adults [71, 72]. SWL should be considered as first-line therapy in children with staghorn calculi in non-dilated collecting systems [73].

SWL performed before PCNL is associated with improved SFR [74]. However, combination or sandwich therapy (PCNL followed by SWL, and if needed second-stage PCNL) still result in an inferior SFR when compared to multi-stage PCNL. Thus, if combination or sandwich therapy is undertaken, consider to do PCNL as the last procedure to remove residual fragments following SWL [4, 75].

Chemolysis

- For patients who are unfit for surgery or decline intervention, chemolysis (stone dissolution therapy) may be an alternative option (GR: B, LE: 2).
- Oral chemolysis can be applied to uric acid stones (GR: A, LE: 2).

Because of a well-established risk of sepsis and electrolyte disturbance associated with chemolysis, precautions should be undertaken prior to any attempts of active intrarenal dissolution therapy for staghorn calculi [20].

Percutaneous chemolysis is presently rarely used, although it has been described as an option for struvite stones. Suby's G solution (10% hemiacidrin; pH 3.5–4) is composed of sodium carbonate, magnesium oxide, and citric acid, which can be used for dissolution of struvite stones [76, 77]. Renacidin can be used for patients with complex struvite stones who are not stone free by surgical stone removal or SWL [78, 79].

Oral chemolitholysis is especially for uric acid stones based on alkalinization of urine to high pH by application of alkaline citrate or sodium bicarbonate. However, higher urine pH for chemolysis might promote calcium phosphate stone formation [80].

Postoperative evaluation, follow-up, and management of residual stones

- Non-contrast computed tomography (NCCT) is recommended to assess final SFR at 4 weeks postoperatively (GR: A, LE: 1).
- Plain abdominal radiograph (KUB) and ultrasonography are adequate to assess stone status in long-term follow up (GR: A, LE: 3).
- Mechanical percussion combined with patient position change (MPPP) may be provided for patients with residual fragments ≤ 6 mm (GR: B, LE: 2).

NCCT has the highest sensitivity to detect residual stone fragments. In patients with BMI < 30, low-dose NCCT has been shown to be as accurate as standard NCCT. Plain abdominal radiography (KUB) and ultrasonography seem to be a reasonable alternative to assess stone activity in long-term follow-up with lower radiation doses than NCCT [81]. The initial SFR may be evaluated with KUB during the first postoperative week, and the final SFR should be evaluated with NCCT at 4 weeks postoperatively [82]. The first follow-up should be performed within 6 months, and for this, KUB and ultrasonography are adequate to assess stone activity. The subsequent follow-up should be performed yearly or sooner based on aggressiveness of stone activity [83].

Historically, residual stones < 4 mm were considered clinically insignificant residual fragments (CIRF). However, ample data have shown that this definition of residual fragments is associated with a relatively high risk of stone-related events, and a cut-off-point of 2 mm may be a better threshold to determine the need for secondary procedures versus observation [84, 85].

SWL or RIRS can be used to treat patients with residual fragments ≥ 6 mm. Mechanical percussion combined with patient position change (MPPP) may be used for patients with residual fragments < 6 mm, especially for the fragments located in the lower pole [86–88]. MPPP can be accomplished in two methods: mechanical percussion, combined with diuresis and inversion therapy (PDI) or external physical vibration with the lithecbole device (EPVL).

Stone recurrence prevention

- Metabolic evaluation should be performed in all patients except those with pure infection stones. (GR: A, LE: 3).
- Long-term antibiotic therapy or urinary acidification therapy may be used for stone recurrence prevention in patients with struvite stones (GR: B, LE: 3).

Stone analysis should be performed in all patients with staghorn calculi [89]. Stone composition will determine if the stone is infectious or metabolic, which in term dictates subsequent prevention strategy [90]. Patients with metabolic stones should undergo metabolic evaluation to direct dietary and/or pharmacologic treatment [91]. Patients with pure infection stones may benefit from long-term antibiotic therapy to sterilize small residual fragments and prevent recurrence and/or infection [21], although this treatment option is controversial, since long-term antibiotics may induce resistance to antibiotics. Some authors recommend 1–2 weeks of full-dose antibiotic therapy followed by suppressive dosing for 3 months [92]. Urine acidification with methionine or ammonium chloride has been shown effective for struvite stone prevention in other series [93, 94]. For severe cases with residual or recurrent struvite stones, long-term therapy with the urease-inhibitor, acetohydroxamic acid (AHA), has been shown effective for stone prevention; however, this treatment has potential serious adverse effects [95].

Conclusion

A series of recommendations regarding the management of staghorn calculi, along with related commentary and supporting documentation offered in the present guideline, are intended to provide a clinical framework for the practicing urologists in the management of staghorn calculi.

Author contributions WZ: data curation, formal analysis, methodology, investigation, writing—review and editing; PO, MP, SC, GM, WZ, ZZ, JG, DS, MM, SKP, IM, SBH, BC, AA, AK, SK, RLS, SG, WG, JL, YL, SF, WK, LY, NB, SA, MA, OD, GK, MM, and ZY: formal analysis, writing—review and editing; PA, KS, and GZ: conceptualization, formal analysis, investigation, project administration, visualization.

Funding Not applicable.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

Human or animal rights The present study adheres to the World Medical Association Declaration of Helsinki Ethical Principle for Medical Research Involving Human Subjects. The protocol is reviewed and approved by the hospital ethical committee. Informed consents are required from all participants.

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