Chapter 1: AUA Guideline on the Management of Staghorn Calculi: Diagnosis and Treatment Recommendations

Background: Staghorn Calculi

Staghorn calculi are branched stones that occupy a large portion of the collecting system. Typically, they fill the renal pelvis and branch into several or all of the calices. The term "partial staghorn" calculus designates a branched stone that occupies part but not all of the collecting system while "complete staghorn" calculus refers to a stone that occupies virtually the entire collecting system. Unfortunately, there is no consensus regarding the precise definition of staghorn calculus, such as the number of involved calices required to qualify for a staghorn designation; consequently, the term "staghorn" often is used to refer to any branched stone occupying more than one portion of the collecting system, ie, renal pelvis with one or more caliceal extensions. Furthermore, the designation of "partial" or "complete" staghorn calculus does not imply any specific volume criteria.

Staghorn calculi are most frequently composed of mixtures of magnesium ammonium phosphate (struvite) and/or calcium carbonate apatite. Stones composed of cystine or uric acid, either in pure form or mixed with other components, can also grow in a "staghorn" or branched configuration, but calcium oxalate or phosphate stones only rarely grow in this configuration. Struvite/calcium carbonate apatite stones also are referred to as "infection stones" because of their strong association with urinary tract infection caused by specific organisms that produce the enzyme urease that promotes the generation of ammonia and hydroxide from urea (Bruce & Griffith, 1981) [2]. The resultant alkaline urinary environment and high ammonia concentration, along with abundant phosphate and magnesium in urine, promote crystallization of magnesium ammonium phosphate (struvite), leading to formation of large, branched stones. Other factors play a role, including the formation of an exopolysaccharide biofilm and the incorporation of mucoproteins and other organic compounds into this matrix. Cultures of "infection stone" fragments obtained from both the surface and inside of the stone have demonstrated that bacteria reside within the stone thereby causing the stone itself to be infected in contrast to stones made of other substances where the stones remain sterile inside [3]. Repeated urinary tract infections with urea-splitting organisms may result in stone formation, and once an "infection stone" is present, infections tend to recur.

Over time, an untreated staghorn calculus is likely to destroy the kidney and/or cause life-threatening sepsis [4, 5]. Complete removal of the stone is an important goal in order to eradicate any causative organisms, relieve obstruction, prevent further stone growth and any associated infection, and preserve kidney function. Although some studies suggest that it may be possible to sterilize small residual struvite fragments and limit subsequent stone activity [6], the majority of studies indicate that residual fragments may grow and be a source for recurrent urinary tract infection [7, 8]. Thus, the Panel believes that complete stone removal should remain a therapeutic goal, especially when a struvite/calcium carbonate/apatite stone is present.

The Panel identified four modalities as potential alternatives, on the strength of the evidence, for treating patients with staghorn calculi:

- **percutaneous nephrolithotomy (PNL) monotherapy;**
- **combinations of PNL and shock-wave lithotripsy (SWL);**
- **SWL monotherapy; and**
- **open surgery** – open surgical exposure of the kidney and removal of stones from the collecting system, typically anatrophic nephrolithotomy.

Please refer to the Appendix 1 hotlink to "Technical Aspects of Active Treatment Modalities" for further details.

Methods Used to Develop the 2004 Guideline

The initial literature database used for the analysis was developed using MEDLINE® and MeSH® headings related to staghorn calculi. The database spanned the period from July 1992 through July 2003 (subsequent to the time period reflected in the 1994 clinical practice guideline) and was limited to human studies published in the English language.

Ninety-six citations were chosen on the basis of key words and recommendations by Panel members. The Panel considered 58 articles to be candidates for data extraction. These 58 articles were divided among the six Panel members, and data were extracted using an updated version of the extraction instrument that was used to develop the 1994 guideline. Most (43 of 58) articles were extracted by a single Panel member, but 26% (15 of 58) of the articles were extracted independently by two Panel members who then reconciled their findings. Double extraction was performed either when an article was in the top quartile with regard to numbers of patients reported or when a Panel member requested a second extraction due to complexity of the data. Thirty-two articles ultimately were included in the final database. Reasons for excluding articles from the final analysis are discussed in Chapter 2 of the full guideline report. The data extraction form and a complete list of included references are available in Appendix 2.

The Panel concluded that the following outcomes are the most significant in establishing guidelines for the treatment of patients with staghorn calculi:

- Percentage of patients who become stone free (stone-free rate);
- mean number of primary, secondary, and adjunctive procedures that patients undergo; and
- frequency of patients having acute complications associated with the chosen primary treatment modality (complication rate).

Stone-free and acute complication data were evaluated using meta-analyses with the confidence profile method developed by Eddy and associates [9, 10] that allows data from studies that are not randomized, controlled trials to be analyzed. A complete description of the data analysis is included in Chapter 2 of the full guideline report. Herein, results of meta-analyses are reported as medians expressed as percentages. These values provide the best estimate of a patient's probability of experiencing the event (being stone free or having an acute complication). The probability (Bayesian) is 5% that the true value is outside the associated 95% confidence interval (CI). Data concerning procedures were evaluated by calculating weighted means across studies, a method that does not produce 95% CIs.

Summary tables were produced for each outcome and treatment modality and were reviewed by the Panel. Additional summary tables stratified by whether stones were partial or complete and by age (adult versus pediatric) also were produced. In analyses stratified by patient age, estimates for pediatric patients were derived from studies or groups that contained only patients <18 years of age. Estimates for adults were from studies or groups that were not exclusively pediatric, including studies or groups with a mixture of pediatric and adult patients. The Panel used these tables to formulate treatment guidelines. A draft guideline report was reviewed and approved by all members of the Panel and was submitted for peer review to 61 reviewers of whom 35 provided comments. Based on peer assessment comments, the guideline was revised and forwarded to the Practice Guidelines Committee and the Board of Directors of the AUA, both of which rendered approval.

Outcomes Analysis

The 2004 outcomes table shows results of statistical analyses of abstracted outcomes data from the treatment literature published between July 1992 and July 2003 related to the four treatment modalities for patients with staghorn calculi. The discussion of overall outcomes is based on the outcomes table and on expert opinion. Instances in which data in the current outcomes table differ substantially from data reported in the 1994 guideline are discussed. The results reviewed for patients with partial versus complete staghorn stones and for pediatric patients are based on additional analyses (which are included in Chapter 3 but are not shown in the outcomes table). Outcomes data for adults are not reported separately herein but are included in Chapter 3.

Stone-free Rates

The overall estimated stone-free rate following treatment is highest for PNL (78%) and lowest for SWL (54%; Figure). Although stone-free rates following PNL and SWL are similar to those reported in the 1994 guideline, the newly calculated rate for combination therapy is substantially lower (81% in 1994 versus 66% currently). This discrepancy probably reflects the fact that at the time the 1994 guideline was developed, the majority of the cases analyzed were based on a combination-therapy approach where PNL was the terminal procedure (generally a three-procedure sequence of PNL-SWL-PNL). However, SWL was the last procedure in a number of the cases in this current analysis, and "second-look" nephroscopy was not performed to assure a stone-free state. The estimated stone-free rate for open surgery is somewhat lower than that reported in the previous guideline (71% versus 82%, respectively). It is notable, though, that the new rate for open surgery is based on only 3 patient groups that include only 51 patients. Additionally, in current practice, open surgical procedures are rarely performed initially except in very complex cases, and a reduced stone-free rate is expected. The rather wide 95% CIs reflect the small numbers of patients included in studies of open surgery.

2004 Outcomes Table

MEDLINE® search: July 1992 through July 2003

	PNL		Combination PNL & SWL		SWL		Open Surgery	
	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)
Stone-free Rate	12 776	78% (74-83%)	6 365	66% (60-72%)	15 392	54% (45-64%)	3 51	71% (56-84%)
Procedures per Patient	Grps Pts	Weighted Mean	Grps Pts	Weighted Mean	Grps Pts	Weighted Mean	Grps Pts	Weighted Mean
Primary	8 462	1.3	4 329	3.0	13 368	2.8	1 32	1.0
Secondary	5 296	0.4	1 105	0.0	9 360	0.2	1 32	0.2
Adjunctive	3 218	0.2	3 229	0.3	10 400	0.6	1 32	0.2
Acute Complications	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)	Grps Pts	Med Prob (95% CI)
Transfusion	6 282	18% (14-24%)	5 426	17% (10-26%)	—	Insufficient data	—	Insufficient data
Death	4 210	0% (0-1%)	1 101	0% (0-2%)	—	Insufficient data	—	Insufficient data
Overall Sig Compl	6 358	15% (7-27%)	6 434	14% (9-20%)	10 354	19% (11-30%)	1 32	13% (4-27%)

Abbreviations: CI=confidence interval; Compl=complications; Grps=groups; Med=median; PNL=percutaneous nephrolithotomy; Prob=probability; Pts=patients; Sig=significant; SWL=shock-wave lithotripsy.

Reported overall significant complications include:

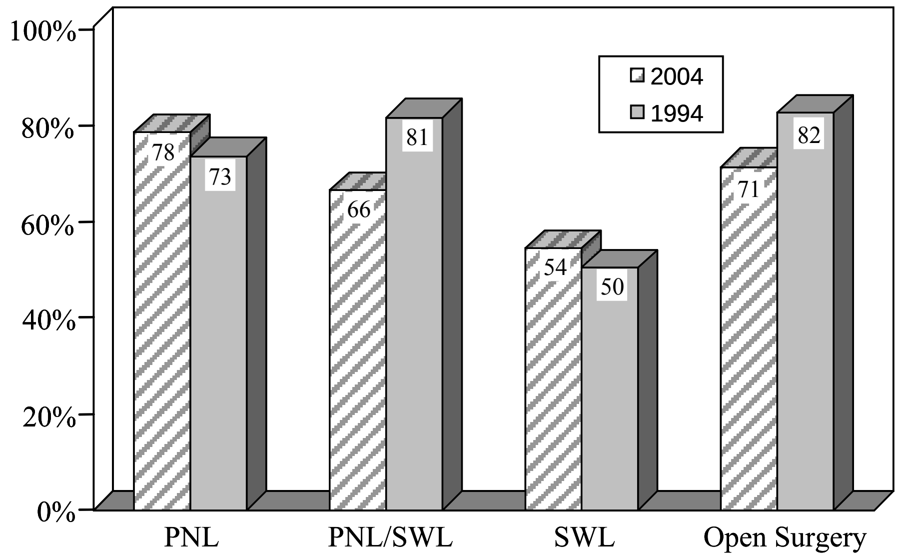
For PNL: acute loss of kidney; colon injury; hydrothorax; perforation; pneumothorax; prolonged leak; sepsis; ureteral stone; vascular injury.

For SWL: acute loss of kidney; colic requiring admission; hematoma (significant); obstruction; pyelonephritis; sepsis; steinstrasse; ureteral obstruction.

For combination therapy: any listed for PNL or SWL plus deep vein thrombosis; fistula; impacted ureteral stones; renal impairment.

For open surgery: acute loss of kidney; persistent sinus tract; persistent urine leak; pulmonary embolism; ureteral obstruction; vascular injury.

Figure. Stone-free Rates: 2004 Guideline versus 1994 Guideline



Abbreviations: PNL=percutaneous nephrolithotomy; SWL=shock-wave lithotripsy.

Procedures per Patient

Several methodological issues need to be clarified with regard to the "Procedures per Patient" section of the 2004 outcomes table. First, secondary procedures are defined as those intended to remove stones while adjunctive procedures include those intended to address complications as well as procedures incidental to the stone removal process (such as stent insertion or stent removal). These definitions are not the same as those used to develop the 1994 guideline where some secondary and all adjunctive procedures were classified as complications. As a result, the 1994 estimates of numbers of procedures were lower. Second, stent insertion or removal is counted as a separate procedure only when not performed during the same session as another primary or secondary procedure. Third, based on experience, the Panel believes that secondary and adjunctive procedures are highly likely to be underreported for all treatment modalities. Fourth, for articles that do not include full information concerning the number of secondary or adjunctive procedures performed, the number is assumed to be unknown rather than zero.

Combining primary, secondary, and adjunctive procedures yields an estimate of the total number of procedures performed. On average, PNL requires 1.9 total procedures while combination therapy and SWL require 3.3 and 3.6 total procedures, respectively. For open surgery, an average of 1.4 total procedures is performed, but this estimate is based on only 32 patients. The increase from the average of 1.0 total procedures related to open surgery reported in the 1994 guideline reflects, at least in part, the fact that this option now tends to be used initially in only the most complex cases.

Acute Complications

Acute complications include transfusion, death, and overall significant complications. The meta-analytic estimated transfusion rate is similar for PNL and combination therapy (<20%). Based on Panel opinion and data from the 1994 guideline, the Panel estimates that the transfusion rate for SWL is very low, but transfusions may be needed for patients who develop clinically significant perirenal hematomas. The transfusion rate for open surgery is estimated by the Panel to range from 20% to 25%.

Death attributable to any of the four treatments is rare but can occur particularly in patients with medical comorbidities or in those who develop sepsis or other significant acute complications. Although insufficient data are available to develop a statistical estimate of the risk of death associated with open surgery, the Panel estimates the death rate to be approximately 1%.

The Panel found considerable variability in reporting complications. For example, patients with fever alone may be classified as septic by some investigators but as having fever by others. Twenty-two specific acute complications ranging from acute loss of kidney to vascular injury are included in the category of overall significant complications (see footnote to the outcomes table). Estimated rates for overall significant complications are similar for the four therapeutic modalities and range from 13% to 19%.

Partial and Complete Staghorn Stones

The classification of staghorn stones as partial or complete is not standardized. Stone-free rates following SWL monotherapy have been found to be highly dependent on stone burden[11]. The present analysis compares stone-free rates for patients with partial versus complete staghorn stones using data from studies with findings stratified by some measure of stone burden. It demonstrates that stone-free rates are substantially higher for each treatment modality in those with partial staghorn stones. In patients treated with PNL, for example, 74% of those with partial staghorn stones and 65% of those with complete staghorn stones are stone free. Sufficient data are available to estimate numbers of primary procedures associated with SWL for those having partial versus complete staghorn stones; on average, those having partial staghorn stones require fewer primary procedures (2.1 and 3.7, respectively). Data concerning complications stratified by stone classification are available in only one study, the results of which suggest that complication rates in staghorn stones are directly proportional to stone burden[12].

Pediatric Patients

Staghorn stones are rare in pediatric patients. No studies reporting results of PNL or combination therapy included only pediatric patients, and data for pediatric patients treated with open surgery are too few to support a valid meta-analysis. The stone-free rate with SWL monotherapy reported by studies including only pediatric patients is 78%, an average of 2.9 total procedures are performed and complications are infrequent.

Treatment Guideline Statements

As in 1994, the present treatment guideline statements are graded with respect to three levels of flexibility: A "standard" has the least flexibility as a treatment policy; a "recommendation" (termed a "guideline" in the 1994 document) has significantly more flexibility; and an "option" is even more flexible. These three levels of flexibility are defined as follows:

1. **Standard:** A guideline is a standard if (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) there is virtual unanimity about which intervention is preferred;
2. **Recommendation:** A guideline is a recommendation if (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred; and
3. **Option:** A guideline is an option if (1) the health outcomes of the alternative interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal.

Index Patient

Standards, recommendations, and options for the treatment of patients with staghorn calculi apply to an "index patient." **In this guideline, the index patient is defined as an adult with a staghorn stone (non-cystine, non-uric acid) who has two functioning kidneys (function of both kidneys is relatively equal) or a solitary kidney with normal function, and whose overall medical condition, body habitus, and anatomy permit performance of any of**

the four accepted active treatment modalities, including the use of anesthesia. For patients who do not meet all of the above criteria, the choice of available treatment options may be limited to three or even fewer of the four accepted active treatment modalities, depending on individual circumstances.

Treatment Guidelines for the Index Patient

Standards

1. A newly diagnosed patient should be actively treated.

It has been clearly demonstrated that, if left untreated, a staghorn stone eventually will destroy the kidney [5, 13]. Patients may experience recurrent urinary tract infection, sepsis, and pain. In addition, the stone has a significant chance of causing death in affected patients [4,5,14,15,16]. Nonsurgical treatment, that is, management with antibiotics, urease inhibitors, and other supportive measures only, is not considered a viable alternative except in those patients otherwise too ill to tolerate stone removal. A retrospective analysis of almost 200 patients with staghorn calculi suggested that renal deterioration occurred in 28% of patients with staghorn calculi who were treated "conservatively [16]."

2. The patient must be informed about the relative benefits and risks associated with the active treatment modalities.

Although, as a practical matter, it is evident that the availability of equipment and the expertise of an individual practitioner may impact the choice of a treatment intervention, it is unacceptable to withhold certain treatments from the patient and not offer them as alternatives because of the physician's personal inexperience or unfamiliarity with the accepted treatment modalities, or because of the local unavailability of equipment or expertise [17].

Recommendations

1. Percutaneous nephrolithotomy should be the first treatment utilized for most patients.

Except for some patients with extremely large and/or complex staghorn stones (see Option 2), PNL-based techniques are preferred because of their lower morbidity compared to open surgery. The only randomized, prospective trial comparing PNL to SWL for staghorn stone management demonstrated stone-free rates with PNL-based therapy to be more than three times greater than with SWL monotherapy [18]. It is the Panel's view that results of other retrospective series of SWL monotherapy for staghorn stones reflect a selection bias in that many or most of the stones included are likely lower-volume stones than in the Meretyk series where such bias was eliminated by the study design (randomized clinical trial). The PNL-based therapy stone-free rates in the Meretyk trial and in the meta-analysis conducted by the Panel parallel the findings and recommendations of the 1994 clinical practice staghorn guideline report [17].

2. If combination therapy is undertaken, percutaneous nephroscopy should be the last procedure for most patients.

The mainstay of combination therapy is endoscopic removal. This approach allows removal of a high volume of stone as well as an accurate assessment of stone-free status. Nephroscopy has been shown to be more sensitive than plain abdominal radiography or nephrotomography for detecting residual fragments [19]. While non-contrasted computed tomography is now considered the gold-standard method for determining stone-free status [20], fragments adjacent to nephrostomy tubes may not be detected with this imaging modality. SWL may be utilized in cases where remaining stones cannot be reached with flexible nephroscopy or safely approached via another access tract. However, total removal of fragments from the collecting system after SWL without subsequent nephroscopy is unlikely. Extremely low stone-free rates have been reported for combination approaches where SWL was the last combination procedure. For example, Segura and associates reported only a 23% stone-free rate with this approach [21]. Therefore, percutaneous nephroscopy should be the last part of a combination therapy sequence as it allows for better assessment of stone-free status and a greater chance of achieving this state.

3. Shock-wave lithotripsy monotherapy should not be used for most patients; however, if it is undertaken adequate drainage of the treated renal unit should be established before treatment.

Results of the meta-analysis of articles published since the 1994 guideline report on staghorn calculi show that SWL produces significantly lower stone-free rates than PNL-based approaches despite the Panel's opinion that most SWL monotherapy series probably include patients with smaller stones than most PNL staghorn series. The Panel's observation is supported by the results of the Meretyk randomized clinical trial [18]. In addition, there is no evidence that newer SWL devices have improved the stone-free rates for patients with staghorn calculi.

If SWL monotherapy is undertaken, adequate drainage of the treated renal unit should be established prior to initiating treatment [22, 23]. Placement of either an internal ureteral stent or a percutaneous nephrostomy tube should facilitate fragment passage, prevent severe obstruction, and limit sepsis following stone fragmentation.

4. Open surgery (nephrolithotomy by any method) should not be used for most patients.

The preference for PNL-based therapy as compared to open surgery for managing the majority of patients with staghorn calculi is based on several criteria. The results of this meta-analysis and those supporting the preceding 1994 guideline indicate that stone-free rates are similar with PNL-based therapy and open surgery. PNL-based therapy has advantages, as patients are not subjected to lengthy incisions, hernia, and eventration of flank musculature [24]. The Panel is unaware of any contemporary studies conducted in the United States comparing duration of recovery for these two approaches. However, it would be expected that PNL-based therapy would be associated with reduced convalescence and perhaps with shorter hospitalizations and reduced narcotic requirements. These differences in outcomes recently have been demonstrated in laparoscopic versus open surgical nephrectomy, suitable surrogates for the aforementioned procedures [25].

Options

1. Shock-wave lithotripsy monotherapy may be considered in patients with small-volume staghorn calculi with normal collecting-system anatomy.

As previously noted, stone-free results in patients undergoing SWL are influenced heavily by stone burden. Patients with small-volume staghorn calculi have significantly higher stone-free rates than do those with larger stones. Stone burdens of <500 square millimeters, particularly in patients with no or minimal dilatation of the renal collecting system, may be considered for SWL monotherapy in conjunction with renal drainage via ureteral stenting or percutaneous nephrostomy [11].

2. Open surgery can be considered for patients in whom the stone is not expected to be removed by a reasonable number of less invasive procedures.

Open surgery is rarely needed to manage patients with staghorn calculi. This approach may be considered in patients with extremely large staghorn calculi, especially in those with unfavorable collecting-system anatomy. Certain abnormalities of the body habitus, such as extreme morbid obesity or skeletal abnormalities, may preclude fluoroscopy and endoscopic therapies, requiring consideration of an open surgical approach. Anatrophic nephrolithotomy is usually the preferred operation in such cases.

Recommendations for Non-index Patients

1. Nephrectomy should be considered when the involved kidney has negligible function.

Some patients with a complex staghorn calculus may demonstrate intractable renal parenchymal disease, with diminished renal function, as a result of persistent obstruction and/or infection. Moreover, this poorly functioning kidney can serve as a source of persistent morbidity, such as recurrent urinary tract infection, pyelonephritis, and sepsis. In fact, the combination of stones, obstruction, and recurrent infection can result in the development of xanthogranulomatous pyelonephritis [5, 13, 26, 27]. In such patients with poorly functioning, chronically infected kidneys, nephrectomy (usually performed when the contralateral kidney is normal) may be the best treatment option to prevent further patient morbidity.

2. Shock-wave lithotripsy monotherapy should not be used for patients with staghorn or partial staghorn cystine stones.

Outcomes for SWL are dependent on stone size, stone location, and stone composition. Although successful SWL has been reported for relatively small cystine stones, SWL monotherapy for large (>25 mm) cystine stones is associated with poor stone-free rates [28, 29, 30, 31]. Bhatta and colleagues identified two types of cystine stones (rough and smooth) that differed in their response to SWL [32]. However, preoperative radiographic distinction between the two types of stones is difficult and has proven to be of limited practical value. While SWL for some patients with small cystine stones may be effective, SWL monotherapy for those harboring large or staghorn cystine stones is not recommended.

Option for Non-index Patients

1. Shock-wave lithotripsy monotherapy or percutaneous-based therapy may be considered for children.

Although limited contemporary data are available, the Panel believes that percutaneous-based therapy is safe and effective in children. In addition, reports show that the stone-free rate in children using SWL monotherapy approaches 80% [22, 33, 34, 35]. Comparative evidence demonstrates that the stone-free rate using SWL monotherapy in children is higher than in adults for large renal stones [36]. This finding may be a result of differing body size, ureteral elasticity and contractility, or ureteral length, though these are unproven factors.

Two issues need to be considered before embarking on SWL treatment in children. First, animal studies have shown that the developing kidney may be more susceptible to the bioeffects of SWL [37, 38, 39]. Second, SWL has not been approved by the U.S. Food and Drug Administration (FDA) for this specific indication. Thus, treatment regimens may deviate from that employed for FDA-approved indications, and this difference should be considered in the risk-versus-benefit assessment.

Discussion

Percutaneous Nephrolithotomy

PNL has emerged as the treatment of choice for the management of patients with staghorn calculi based on superior outcomes and acceptably low morbidity. Recent advances in instrumentation and technique have improved stone-free rates, increased treatment efficiency, and reduced morbidity thereby favoring PNL monotherapy.

The trend toward PNL monotherapy has been driven in part by the expanded role of flexible nephroscopy, better grasping devices and baskets, the holmium laser for intracorporeal lithotripsy, and also the use of multiple percutaneous access tracts. At the time of initial PNL, flexible nephroscopy is used after debulking the stone with rigid nephroscopy to remove stones remote from the percutaneous access tract. If residual stones are identified on post-PNL imaging studies, second-look flexible nephroscopy via the preexisting nephrostomy tract is used to retrieve residual stones. However, it also may be necessary to place other tracts in this setting to facilitate complete stone removal.

In addition to its role in retrieving residual calculi and achieving a stone-free state, flexible nephroscopy also may limit the need for additional percutaneous access tracts. Wong and Leveillee treated 45 patients with partial or complete staghorn calculi via a single percutaneous access using flexible nephroscopy and holmium:yttrium-aluminum-garnet (YAG) laser lithotripsy in conjunction with rigid nephroscopy for percutaneous debulking [40]. With this approach, a stone-free state was achieved in 95% of patients with a mean of 1.6 procedures per patient.

Although initial stone debulking traditionally relied on ultrasonic energy, pneumatic lithotripsy likewise provides a rapid, efficient means of fragmenting stones. Recently, a combination device has been developed that incorporates ultrasonic and pneumatic lithotripsy in a single instrument in which the two modalities can be used simultaneously or alone. This device has the potential to increase the speed and versatility of rigid nephroscopy [41].

Limitations of Shock-wave Lithotripsy

The current recommendations suggest that percutaneous-based therapy should remain the mainstay for management of staghorn calculi. The Panel believes that SWL monotherapy has a very limited role in the management of patients with complex renal calculi and should be reserved for use in pediatric patients or in low-volume staghorn calculi. Indeed, previous research [12, 22, 42, 43, 44] as well as the current meta-analysis suggest that SWL monotherapy can achieve significantly higher stone-free rates in patients with partial staghorn calculi as compared to those individuals with the stones filling the entire renal collection system. Moreover, the need for secondary procedures and postoperative complications are reduced substantially in patients with partial staghorn stones treated with SWL as compared to those with complete staghorn calculi.

SWL monotherapy for patients with staghorn calculi can result in significant postoperative complications, including steinstrasse, renal colic, sepsis, and perinephric hematoma. In addition, animal studies have suggested that adverse effects to the kidney may not be solely a result of the mechanical forces (shear, stress, cavitation) of the acoustic wave on the renal parenchyma but also a result of free radical-induced cellular injury as well as renal vasoconstriction [45, 46, 47, 48, 49].

Combination Therapy

Combination therapy was recommended as the treatment of choice for patients with staghorn calculi by the original Nephrolithiasis Guideline Panel in 1994 [17], but there has been little uniformity in the literature with regard to what constitutes combination therapy. The original intent of this approach was to initiate therapy with percutaneous debulking, followed by SWL of residual stones, and finally percutaneous nephroscopy to retrieve the remaining fragments ("sandwich therapy"). In many cases, however, final percutaneous nephroscopy has been abandoned in favor of spontaneous passage of fragments, resulting in suboptimal stone-free rates in some series.

Currently, more aggressive use of flexible nephroscopy has resulted in less reliance on adjuvant SWL, improved stone-free rates, and fewer procedures per patient. Comparing PNL with combination therapy, the Panel found stone-free rates are higher with PNL (78% versus 66%, respectively) and that PNL requires fewer total procedures (1.9 versus 3.3, respectively); transfusion rates are similar for the two modalities (18% versus 17%, respectively).

Open Surgery

With today's newer technologies, open surgery is rarely required to manage patients with nephrolithiasis. In 2000, only 2% of Medicare patients undergoing a stone-removing procedure were treated with open surgery [50]. Moreover, tertiary medical centers now are reporting that the approach is used in <1% of patients undergoing stone removal [50, 51]. The current indications for open surgery in patients harboring staghorn calculi are extremely large stones, complex collecting system issues, excessive morbid obesity, or extremely poor function of the affected renal unit.

Lam and associates reported that only 54% of patients with giant staghorn calculi (>2500 mm^2) became stone free with PNL-based therapy and that only 68% of those with staghorn calculi in grossly dilated collecting systems were rendered stone free with this approach [11]. These results are inferior to those achieved in their patients with smaller staghorn stones in less complex collecting systems. Assimos and colleagues reported that stone size and collecting-system anatomy have less influence on stone-free status when an open surgical approach is undertaken [52]. Nephrolithotomy may be considered in these rare cases as it will allow the best chance of a stone-free state, and it permits concomitant reconstruction of the renal collecting system. Some extremely obese individuals also may require this approach as their body habitus precludes fluoroscopic imaging and endoscopic maneuvering required for PNL. Successful laparoscopic nephrolithotomy has been performed in a porcine model and also in humans [53] but not in patients harboring complex staghorn calculi. It is not anticipated that laparoscopy will become a suitable treatment approach for this unique cohort of patients in the near future. Patients with staghorn calculi in a nonfunctioning kidney are candidates for nephrectomy, and the procedure also may be considered if the stone-laden kidney has irrevocably poor function providing the contralateral renal unit has satisfactory function. Laparoscopic nephrectomy is an option, but open surgical nephrectomy may be a safer approach if there is intense perirenal inflammation, such as that which occurs with xanthogranulomatous pyelonephritis [54, 55].

Alternative Treatments

Several modalities for treating staghorn stones examined by the Panel were felt not to have sufficient evidence to support their inclusion in the 2004 guideline. These modalities include chemolysis, ureteroscopy, other combination modalities, and laparoscopic stone removal. Irrigation of the collecting system with solutions such as Renacidin® to dissolve struvite staghorn stones, either as a primary technique or after PNL, may be effective but requires prolonged hospitalization and is not widely used. Ureteroscopy is very useful for removing ureteral fragments remaining after primary treatment of the staghorn stone and has the advantage of being an outpatient procedure. While there have been some favorable reports of ureteroscopy monotherapy for low-volume staghorn stones, multiple procedures are required [56, 57]. Given the inability to physically extract fragments larger than a few millimeters, ureteroscopy is not an efficient primary technique for staghorn stones. Ureteroscopy as an adjunct to PNL for staghorn stones may have value, however, and ureteroscopy in combination with PNL has also been reported [58].

Surveillance and Medical Management

The management of patients with staghorn calculi continues after stone removal as these patients are at risk for stone recurrence. Streem and associates reported that ipsilateral stone recurrence developed in 22.8% of patients with high-volume or staghorn calculi at a mean follow-up of 40.5 months after combined PNL and SWL therapy [59]. Measures to attenuate future stone activity should be undertaken, and stone analysis should be the initial step. If the stone is composed of any non-struvite/calcium carbonate apatite components, 24-hour urine testing is indicated. That such testing is usually not necessary in those with pure struvite/calcium carbonate apatite stones is supported by the investigations of Lingeman and colleagues, who found that only a small percentage of these patients had a definable metabolic abnormality [60]. Medical therapy may be appropriate for patients with metabolic abnormalities to limit stone recurrence [61]. Patients harboring struvite/carbonate apatite stones may still be at risk for recurrent urinary tract infection after stone removal [59]. Therefore, prophylactic or suppressive antibiotic therapy is a consideration for this cohort. Patients with abnormal lower urinary tracts (for example, neurogenic bladder or urinary diversion) undergoing removal of infection-related calculi are at highest risk for stone recurrence [62], and a more aggressive approach, such as the utilization of the urease inhibitor acetohydroxamic acid, is a consideration for this cohort [63].

Limitations of the Literature and Areas for Future Research

Limitations to the process of developing the treatment guideline became apparent during the Panel's review of the literature. Most obviously, there is no uniform system of categorizing staghorn calculi, no standard method of describing the collecting-system anatomy and no widely utilized system for reporting the size of staghorn calculi. Although the most valid data for a meta-analysis are generated by randomized, prospective studies, only one such study was available for this analysis, one more than for the previous guideline project. There also are limited published data on long-term treatment outcomes for this patient cohort, and the long-term data reported are not presented using a standardized system. Further uncertainty stems from differences in health care delivery systems in various countries that may impact the outcomes reported in the literature. Variability in the data leads to uncertainty in outcome estimates, which leads to flexibility in guidelines, a limitation that applies to a variety of outcomes.

There are several areas that the Panel believed should be the focus of future investigations:

- further define the pathophysiology of lithogenesis, especially struvite stone formation;
- further develop methods to predict SWL outcomes;
- develop more effective methods to prevent further stone activity after stone removal;
- improve endoscopic and SWL technology;
- develop pharmacologic methods to manipulate collecting system activity and promote stone passage after SWL;
- develop further strategies to attenuate SWL tissue damage;
- develop methods to facilitate endoscopic skill acquisition; and
- develop additional methods to limit the surgeon's exposure to radiation and bodily fluids and to minimize the surgeon's risk of neuromuscular injury.

In addition, the Panel made the following suggestions to improve research methodologies and reporting:

- rigorously compare various treatment modalities in prospective, randomized, controlled trials;

- develop standardized methods to define renal anatomic and stone characteristics;
- standardize the methods for and timing of determining stone-free status;
- report data stratified by patient/stone characteristics, such as patient age, stone size and composition, and by treatment modality;
- utilize standardized methods to report acute and long-term outcomes;
- standardize the definitions of primary, secondary, and adjunctive procedures; definitions used in this 2004 guideline may be considered;
- develop a disease-specific quality-of-life instrument; and
- provide measures of variability, such as standard deviation, standard error, CI, or variance, when average numbers of patients or procedures are reported.

Appendix 1. Technical Aspects of Active Treatment Modalities

Introduction

This Appendix to the 2004 *Report on the Management of Staghorn Calculi* reviews the four modalities acceptable as potential alternatives for treating patients with staghorn calculi. These modalities are:

- Percutaneous nephrolithotomy (PNL) monotherapy;
- combinations of PNL and shock-wave lithotripsy (SWL);
- SWL monotherapy; and
- open surgery – open surgical exposure of the kidney and removal of stones from the collecting system, typically anatrophic nephrolithotomy.

Percutaneous Stone Removal

Percutaneous nephrolithotomy, which became popular as a primary technique for stone removal in the early 1980s, can be used for most stones. While SWL is still used in the majority of situations involving smaller renal stones, current evidence suggests that patients with staghorn calculi are best managed with PNL-based therapy either as a single technique or in combination with SWL.

PNL is usually performed with the patient in a prone position and may be divided into two components, access and stone removal. To achieve percutaneous access, the urologist or radiologist places a small coaxial needle into the kidney and then manipulates a flexible guide wire though the needle sheath under fluoroscopic or ultrasound guidance into the kidney and down the ureter. Care is taken to choose the optimal port of entry into the kidney. Upper pole entry usually provides access to the majority of the collecting system and may allow complete removal of a staghorn stone through one site [40]. However, two or more access sites may be required when the collecting-system anatomy is complex.

Once access is achieved, the tract is dilated to 24 to 30 French with a balloon or coaxial dilators. Initial fragmentation is performed with a rigid nephroscope using an ultrasonic or pneumatic lithotrite or with a lithotrite that combines both modalities. Sterile saline is used for irrigation. Flexible nephroscopy then is used to access stones that cannot be reached with the rigid nephroscope. Stone fragmentation is undertaken with a holmium:yttrium-aluminum-garnet (YAG) laser or electrohydraulic lithotripsy, and fragments can be removed with flexible instruments. Historically, a 20 to 24 French nephrostomy tube has been placed at the end of the procedure. Some investigators have used smaller nephrostomy tubes in an attempt to reduce postoperative morbidity while others have advocated placing an internalized ureteral stent and not using a nephrostomy tube [64, 65, 66].

Percutaneous nephrolithotomy has many advantages: (1) If the stone can be seen, it can almost always be removed; (2) the collecting system can be inspected directly so that small fragments can be identified and removed; (3) because the tract can be kept open indefinitely, repeated inspections are possible; and (4) success or lack of success is usually readily apparent. More recently, the increased use of flexible nephroscopy and holmium laser lithotripsy has decreased the number of accesses needed to remove staghorn stones.

Hospitalization ranges from one to five days, depending on regional variations, practice patterns, the need for secondary procedures, and patient comorbidities. Most patients resume normal activities one to two weeks after removal of all drainage tubes (nephrostomy tube or stent). Postprocedure tube management also varies among urologists, with some removing the nephrostomy tube immediately, some within 24 to 48 hours and some five to seven days later.

Most complex stones require nephrostomy tube drainage for at least 24 to 48 hours. Based on Panel data, stone-free rates of 74% to 83% are achievable using PNL while transfusion rates range from 14% to 24%. The need for further PNL procedures varies from 10% for simpler stones to up to 50% for more complex stones, and Panel data indicate that patients average 1.3 PNL procedures.

Combination Percutaneous Nephrolithotomy and Shock-wave Lithotripsy

Some patients are best managed by using both PNL and SWL. This approach combines the main advantages of the two techniques by using PNL to rapidly remove large volumes of stone and by using SWL to fragment stones that are difficult to access with PNL.

PNL is undertaken initially, and every effort is made to remove as much stone as possible before proceeding with SWL. Experience has demonstrated that passage of all fragments does not occur following SWL. Therefore, the Panel recommends that the final procedure in combination therapy should be percutaneous nephroscopy. The Panel also notes that combination therapy is being used less frequently as a result of improvements in endoscopic and intracorporeal lithotripsy technology. The Panel believes that repeat PNL, or second-look nephroscopy through an established tract, may prove more efficient for complete stone removal than the combination approach. Some of the recent series have omitted the second-look PNL, and this change in technique likely accounts for the lower current stone-free rate compared to that reported in the original 1994 staghorn guideline document.

Shock-wave Lithotripsy

SWL is commonly used to treat many patients with nephrolithiasis. SWL is based on the principle that a high-pressure shock wave releases energy when passing through areas of different acoustic impedance. Shock waves generated outside the body can be focused onto a stone using a variety of techniques. The shock wave passes through the body and releases its energy as it passes into the stone. Hundreds, or sometimes thousands, of such shock waves are required to adequately fragment stones.

Many different shock-wave machines are available today. While the source for generation of shock waves, shock-wave focusing, and localization techniques have been updated in many second- and third-generation lithotriptors, the basic concept remains the same, ie, to produce an acoustic shock wave that can be focused at a specific location for stone fragmentation. The original lithotripter, the Dornier HM-3, still is utilized, but newer, second- and third-generation devices have been designed with variable power capabilities as well as smaller focal regions, which have resulted in less need for general or regional anesthesia during SWL administration. Nevertheless, these smaller focal zones have resulted in inferior stone fragmentation as compared to the Dornier HM-3 device. Moreover, the higher power density created by some of the second- and third-generation machines has been reported to increase the potential for postoperative complications, including the incidence of clinically significant perinephric hematoma and need for transfusion [67, 68].

SWL is widely available, and its noninvasive nature has much appeal. SWL monotherapy has disadvantages, however, in the management of patients with staghorn stones. In these patients, the Panel found that SWL is associated with a higher risk of residual fragments and a higher probability of unplanned procedures than PNL. In patients with staghorn calculi, such additional interventions as well as the need for multiple SWL procedures may make this approach more inconvenient for patients and more expensive than the other alternatives [69].

Investigations into improving stone fragmentation while minimizing renal damage currently are under way at several institutions. Allopurinol, a free radical scavenger, has been demonstrated in an animal model to significantly reduce the amount of conjugated dienes produced as a result of SWL, thereby diminishing the amount of renal damage that occurs secondary to lithotripsy treatment [48]. This agent also has been shown to attenuate shock-wave-induced renal injury in humans [70].

Furthermore, modifications to the elliptical reflector of the HM-3 lithotripter have been demonstrated in vivo to be effective in fragmenting stones and limiting tissue damage [71]. A piezoelectric annular array (PEAA) generator has the benefits of controlling the collapse of cavitation bubbles produced by the generator and increasing the fragmentation of stone phantoms by 60% [72]. A dual-pulse lithotripter, with two shock-wave sources facing each other triggered simultaneously, has been developed in an attempt to improve stone fragmentation [73]. Clinical studies will determine if these modifications to currently available shock-wave devices will improve stone fragmentation while reducing concomitant renal injury.

In addition, recent in vitro animal and clinical studies suggest that the rate of shock-wave administration can influence stone fragmentation and resultant clearance of stone fragments [74, 75]. These studies have demonstrated that a slower shock-wave rate can significantly improve stone-free rates and may have application for SWL monotherapy in patients with staghorn calculi.

Recent studies also suggest that pretreatment with shock waves at low energy can significantly reduce tissue effects during SWL. This principle is based on the finding that low-energy shock waves that cause minimal tissue injury will induce vasoconstriction, which limits parenchymal injury (Lingeman et al., 2003) [76, 77].

Open Surgery

Open surgical removal of staghorn calculi was at one time considered the "gold standard" to which all other forms of stone removal were compared. Currently, open surgery is performed infrequently with the procedure being used in <1% of patients undergoing stone removal. Open surgery is used most commonly to manage patients with complex staghorn calculi [51].

A number of open surgical procedures have been developed to remove branched stones including extended pyelolithotomy, radial nephrotomy, and anatrophic nephrolithotomy. At present, anatrophic nephrolithotomy is the most appropriate procedure for patients requiring open surgical stone removal. Candidates for the procedure should have extremely large stones and complex collecting-system anatomy. Alternative open surgical approaches would be inferior in this setting [51, 78].

Anatrophic nephrolithotomy usually is performed with the patient in the flank position. A standard flank incision is made, and frequently a lower rib is resected. The anatrophic plane is defined by transiently occluding the posterior segmental artery and administering methylene blue to the patient intravenously. Ischemic hypothermia is instituted. A nephrotomy is made through the anatrophic plane, and the stones are removed. Intraoperative radiography is used to confirm a stone-free state. The collecting system subsequently is reconstructed to correct infundibular stenosis. The collecting system and renal capsule then are closed using absorbable suture. If the patient has had previous renal surgery, the operation may be more difficult [79]. In addition to the usual morbidity associated with surgery, flank incisions are painful, and many patients complain of numbness, paresthesia, and weakness of the abdominal wall resulting in bulging, which may be unsightly [24]. The usual postoperative disability is six weeks.

Patients with staghorn calculi in a nonfunctioning kidney are candidates for nephrectomy. Moreover, nephrectomy may also be considered if the stone-laden kidney has poor function providing the contralateral renal unit has satisfactory function. Laparoscopic nephrectomy is an option, but open surgical nephrectomy may be a safer approach if there is intense perirenal inflammation that may occur with xanthogranulomatous pyelonephritis [54, 55].

Adjunctive Procedures

Percutaneous nephrostomy tube placement may be necessary at any point in the management of patients with staghorn stones. It is a routine part of PNL and frequently is used before or after SWL monotherapy. Internalized ureteral stents are frequently placed in patients with staghorn calculi before SWL monotherapy. The stent is left indwelling to maintain drainage while fragments pass.

In the past, some have advocated irrigations of the collecting system with solutions (chemolysis) such as Renacidin® (Guardian Laboratories, Hauppauge, NY) to dissolve remaining struvite stone fragments, particularly after PNL or SWL monotherapy. Chemolysis currently is not commonly utilized as it prolongs hospitalization. The Panel did not find sufficient evidence in the literature to support the routine use of Renacidin irrigations to eradicate residual struvite fragments.

Ureteroscopy occasionally is necessary to remove retained ureteral stone fragments that are too large to pass spontaneously. While there have been reports of ureteroscopy monotherapy for patients harboring low-volume staghorn stones, multiple procedures are required, and stone-free rates are lower than those achieved with PNL-based therapy [56, 57]. However, the utilization of both PNL and ureteroscopy in patients with staghorn stones has been reported to be successful [58]. Successful laparoscopic neprolithotomy has been performed in a porcine model and also in humans [53] but not in patients harboring complex staghorn calculi. It is not anticipated that laparoscopic approaches will become a suitable treatment approach in patients with complex staghorn stones in the near future.