Complications and treatment aspects of urological stone surgery

Wagenius, Magnus

2021

Document Version:
Publisher's PDF, also known as Version of record

Complications and treatment aspects of urological stone surgery

Magnus Wagenius

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Gamla Barnsjukhuset, Bergaliden 20, Helsingborg. Friday October 1, 2021, 10:00 am

Faculty opponent
Professor
Ralph Peeker
Sahlgrenska Universitetssjukhuset, Göteborg

Organization LUND UNIVERSITY	Document name Doctoral dissertation
	Date of issue 2021-09-09
Author(s) Magnus Wagenius	Sponsoring organization

Title and subtitle

Complications and treatment aspects of urological stone surgery

Abstract

The main focus of this thesis is urological stone treatment. The studies are clinical cohort studies focusing on treatment effects and complications relating to most surgical stone treatments. These studies can be specified as follows: 1.ESWL -Extracorporeal shockwave lithotripsy, 2.URS -Ureteroscopy, 3. PCNL -Percutaneous nephrolithotomy, 4. To evaluate factors affecting SFR such as age, stone size, skin-to-stone distance and mean attenuation value on ESWL treatment results.

Method: Articles 1-3 included all patients receiving stone surgery at the Urology Clinic in north-western Skåne County (Helsingborg/Ängelholm Hospital) between 2009 and 2015. Consecutive ESWL, URS and PCNL treatments between 2009 and 2015. ESWL n=1838, URS n=568, PCNL n=186. In article 4 we included all ESWL treated patients in the same cohort/region between 2016 and 2019 (n=723).

Results. Paper 1: We conclude that there are few complications to modern ESWL treatment. 1 Hz should be used to reduce complications (p=0.025). As there is no indication that 1Hz is less effective than 1.5 Hz, this strongly implies that 1 Hz should be the usual frequency.

Success rate with ESWL alone was high 71.8% (n=1324). Our data indicate that diabetes and larger stone size increase the risk of complications. The need for antiemetics during ESWL is a factor that deserves special considerations and further study. Distal stones seem to have a lower risk of complications (p=0.017).

Paper 2: URS in a modern setting provides excellent results with high SFR and low morbidity. Preoperative stone size <4mm showed 100% SFR success rate (n=112). SFR for stones >4≤6 mm was 96.2% (n=176), for stones >6≤10 mm 84.6% (n=193), and for >10 mm was 68.2% (n=30). Time of day or the presence of urological specialized operating nurse does not affect the risk of complications and we found no other significant risk factors for complications. Regarding bacteria, *E. coli* is the most common in preoperative cultures. In this study the risk of complications increases with age. We conclude that for patients >65 years this should be considered in preoperative counselling.

Paper 3: Stone free rate was 65.6% (n=122), which is acceptable and comparable with other studies. This study had a total complication rate of 16%, of wich 10% were severe. The most common complication to PCNL was infection 60% (bleeding 5.4%, reoperation 1.6% and pain 0.5%). Our results regarding levels of *E. faecalis* in cultures should be validated in a larger cohort, possibly with a higher rate of antibiotic resistance, before a change of guidelines regarding prophylactic antibiotics could be proposed. We conclude that the high prevalence of *E. faecalis* needs to be considered.

Paper 4: (Manuscript) We conclude that stone size and age are the strongest predictors for SFR in ESWL treatment. SSD and HU fail as predictors in our study. We present a simple prediction tool for SFR. We conclude that age and stone size should be taken into consideration when counselling the patient and deciding on treatment modality for patients with urological stones.

Key words

ESWL, URS, PCNL, kidney stone, stone surgery, stone treatment, stone epidemiology, urology

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN and key title 1652-8220 Complications and treatment aspects of urological stone surgery		ISBN 978-91-8021-101-7
Recipient's notes	Number of pages 90	Price
	Security classification	

Signature  Date 2021-08-23

Complications and treatment aspects of urological stone surgery

Magnus Wagenius

LUND
UNIVERSITY

Cover illustration by Henrik Wagenius

Lund University
Faculty of Medicine
Department of Clinical Sciences Lund

ISBN 978-91-8021-101-7
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2021

To Johanna

Table of contents

Abbreviations

AI	Artificial Intelligence
AUC	Area under curve
ESWL	Extracorporeal Shock Wave Lithotripsy
ESBL-CARBA	Extended Spectrum Beta-Lactamase-Carbapenemer, genes causing bacterial resistance to these antibiotics
Ch/CH	Charrièr =circumference in millimetres (3mm=3Ch)
CROES	Clinical Research Office of Endourological Society nomogram (see GSS/STONE)
CT	Computer Tomography
CT KUB	Computed tomography of Kidneys, Ureters and Bladder
CTU	CT urography
EAU	European Association of Urology
EHL	Electrohydraulic
ER	Emergency room
F/Fr/Fg	French gauge=3 times the diameter of a circular catheter (almost the same as Ch)
FTIR	Fourier transform infrared spectroscopy
Gy	Gray=absorption of one joule of radiation energy per kilogram of matter
GP	General Practitioner
GSS	Guy's Stone Scoring, describing stone complexity before PCNL surgery
HM	Human Model
HU	Hounsfield Units
ICU	Intensive Care Unit
In	Inch=based on the metric system and defined as exactly 25.4 mm
Indinavin®	A HIV medication causing "X-ray invisible stones"
IVP	Intravenous Pyelography
IRS	Infrared Spectroscopy
LASER/ laser	Light Amplification by the Stimulated Emission of Radiation
L1	Lumbar nerve-segment, se Th.
MAV	Mean attenuation value
MET	Medical expulsive therapy
mm	Millimeter is a unit prefix in the metric system denoting a factor of one thousandth (10−3)
MR/MRI	Magnetic Resonance Imaging

NO	Nitric oxide, free radical and important signaling molecule
NSAID	Non-steroidal anti-inflammatory drugs
PCNL	Percutaneous Nephrolithotomy
PFTE	Hydrophilic polymer, polytetrafluoroethylene
Prostaglandin E2	Important molecule in the inflammatory response
PKD	Polycystic kidney disease
PUJ	Pelvi-Ureteric Junction
RCT	Randomized controlled trial.
RTA	Renal Tubular Acidosis. Deficiency of excreting acid through the kidney. Alkaline urine.
SSD	Skin-to-stone distance
SVF	Standardized Care Procedures
SVF-makrohematuri	Investigation when patients present with makrohematurie includes urine cytology, cystoscopy and CT-IVP scan of the upper urinary tract.
SFR	Stone Free Rate, here and in most articles <4mm stone fragments.
STONE	Nephrolithometry scoring system, describing stone complexity before PCNL surgery
Sv	Sievert=a measure of the health effect of ionizing radiation on the human body
Th	Thoracic: in this context nerve-segment/dermatome. Numbers relates to vertebra where nerve leaves the medulla.
URS	Ureteroscopy
Xanthine stones	Stones derived from a genetic deficiency of xanthine oxidase
XRD	X-ray powder diffraction crystallography.

List of papers

I. Complications in Extracorporal Shock Wave Lithotripsy (ESWL): A cohort study. Magnus Wagenius MD, Jon Jakobsson MSc, Johan Stranne MD, PhD, Adam Linder MD, PhD. Scandinavian Journal of Urology.

II. Ureteroscopy: A study of clinical complications and possible risk factors for stone surgery - a population based study. Magnus Wagenius MD, Mattias Rydberg MSc, Marcin Popiolek MD, Andreas Forsvall MD, Johan Stranne MD, PhD, Adam Linder MD, PhD. Central European Journal of Urology.

III. Percutaneous nephrolithotomy and modern aspects of complications and antibiotic treatment. Magnus Wagenius MD, Jasmine Borglin MSc, Marcin Popiolek MD, Andreas Forsvall MD, Johan Stranne MD, PhD, Adam Linder MD, PhD. Scandinavian Journal of Urology.

IV. Facors influencing stone free rate of Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study. Magnus Wagenius MD, [b]Karl Oddasson MSc, [b]Andras Forsvall MD, [b]Maria Utter MD, [c]Marcin Popiolek MD, [d]Karl-Johan Lundström MD, PhD, [a]Adam Linder MD, PhD. Manuscript.

Tack

Det är många som jag har att tacka för att resultatet av min forskning nu kan läggas fram. Ett varmt tack till er alla även om ni inte nämns – ingen är glömd av mig. Men utöver detta vill jag ändå nämna ett par personer vars stöd varit särskilt betydelsefullt för mig. Adam Linder, min handledare och nära vän genom livet, som gjort mitt forskningsarbete möjligt och meningsfullt. Tack också till mina urologvänner Rolf Lundgren, Ola Bratt, Johan Stranne, Karl-Johan Lundström, Andreas Forsvall och Johan Styrke. Tack min ”sten-mentor” Svante Boson, min bakteriolog-vän Martin Sundqvist och Simon Heissler. Tack till min bror Henrik för de fina illustrationerna och till min far Christer och mor Kristina för språklig hjälp med texten och en fin uppväxt. Tack till mina svärföräldrar Jan och Eva för era kloka synpunkter

Avslutningsvis tack till min hela min familj; barnen Elsa, Klara, Frida och Julia samt speciellt min hustru Johanna, som i allt ger mening åt min tillvaro och som jag fått försumma en hel del för att också få plats med föreliggande arbete.

"Tell me and I forget. Teach me and I remember.

Involve me and I learn." -Benjamin Franklin

"The way to get started is to quit talking and begin doing." -Walt Disney

Introduction

The excruciating pain of a kidney stone causing obstruction is something that has to be experienced to be fully understood. Early May, some years ago, I woke up at dawn, with a dull backpain and a need to void. In the bathroom, the pain became so intense that I collapsed on the floor. I managed to crawl back to my bed, moaning in pain. My wife woke up and pointed out to me that I probably had a kidney stone attack, asked me to moan in a quieter way or I would wake the children.

For at least the past 5 000 years our civilisations have been trying to find a cure to address the suffering of stones in the urinary tract [1, 2]. Kidney stones are common globally[3]. The prevalence rate globally is 5.6% (0.26%-18.5%), and the incidence is 114-720/100 000 individuals. According to epidemiological data from seven Western countries, the incidence and prevalence of urolithiasis are increasing [4, 5]. Prevalence of urolithiasis in Western countries ranges from 8 to 19% in males and from 3 to 5% in females [6]. The age when stone disease peaks is between 40 and 50 years. The percentage of stones accidentally found in the population (asymptomatic) is estimated to be around 3% [4].

In Sweden the male prevalence of urolithiasis was 10% and the incidence was 1-2% in the 1970s. The prevalence in females at the same time was 3% and the incidence was 0.5% [7]. The number of patient visits registered and diagnosed with kidney stones in Sweden has increased from 16,654 (2008) to 25,991 (2019): an increase of 56% [8]. There is still a gender difference but this is starting to equalize [9]. The recurrence of urolithiasis within 10 years has been reported to be 26% in first-time stone formers [10]. We can now treat stones within the urinary tract and minimise morbidity and mortality for patients with kidney stones.

Kidney stones

The simple way to explain how kidney stones are created is described by pouring salt into a glass of water. Initially it forms a solution, but if you keep adding salt a saturation will occur and the salt will start to reappear at the bottom of the glass. To again reach a solution, just add more water. This is also a recommendation to all recurrent urinary stone patients: add more fluid to your daily intake and decrease the risk of stone formation. When described scientifically, stone formation has phases: first the formation of a nucleus, then the aggregation of materials and thereafter the "holding of its position" to enable more growth. All is affected by the levels of stone constituents appearing in urine, the amount of water excretion, the pH, promoters and finally inhibitors [3].

To have an impact on recurrent stone formation we try to disrupt these processes. As urological surgeons we extract or crush the stones causing problems.

Spontaneous crystallization is uncommon even when urine is a supersaturated fluid. In the creation of urine, supersaturation is a natural way for the kidney to work with the electrolytes or salts. This is normal in the loop of Henle (where urine is refined in the kidney) and may lead to calcium phosphate accumulating interstitially in the inner medulla. When or if these deposits become extensive enough to be visible macroscopically we call them Randall's Plaques [11]. Urine is not generally supersaturated and the mechanisms preventing stone formation are stronger than the ones promoting it [12-15].

Stone structure is like most things in nature: simple, but in a complex way – a comparison with sand and cement forming concrete could be used. Stones contain a mixture of crystals/particles (sand) and binding agent/organic matrix (cement). The crystals being calcium, oxalate etc., the matrix containing proteins, lipids, polysaccharides, and other cell-derived material [16, 17].

Crystallization can be influenced by the presence of other crystals, cells, or foreign-bodies [18]. When a stone is formed it starts with *nucleation* constituting crystals from the urine (calcium, phosphate, oxalate etc.).

Aggregation of crystals and the organic matrix interacting with the kidney´s pelvis structures speeds up this process. However, the kidney function works against stone formation, as rapid washout of urine from the kidney and ureter normally prevents stones from forming by "flushing" everything clean. *Crystal growth:* If the crystals

are retained within the pelvis or collecting system, over time this can promote further growth and could lead to the formation of a clinically significant stone. An increased excretion of stone constituent molecules, an alteration in urine pH, reduced urine volume, remaining at the site of formation or a combination of these factors and, of course, time are needed for the stone to form [3, 19].

Stones can be classified in many different ways. A pragmatic way is based on how they are formed.

Non-infectious stones: Calcium oxalate/phosphate and uric acid stones.

Infectious stones: Magnesium ammonium phosphate, ammonium urate and carbonated apatite.

Genetically caused stones: Defects in protein metabolism like cystine and xanthine stones.

Drug induced stones: For example, Indinavir® stones.

A surgical way of classification is by referring to factors that influence the need for surgical action to treat the stone. The first thing to consider is if the stone will be a problem for the patient. The main factors being the *stone-size, location and does it or could it cause obstruction?* If the stone size is larger than around 6mm, something usually needs to be done about it. Smaller stones (≤5mm) can often be left without treatment because most will pass spontaneously [20]. Many other factors have an impact on what method to choose when removing the stone and this will be discussed later.

Stone composition

The majority of stones are composed of calcium-oxalate/calcium-phosphate (≈80%), followed by uric acid (≈10%), infectious stones (≈9%, carbapatite/struvite) and other molecules (1%, cysteine being one of those) [21, 22]. Infectious stones are formed in the presence of urease-producing bacteria, sometimes growing quickly to large stones called "staghorn calculi" [23, 24]. There is a geographical difference in the probability of forming stones: 1-5% in Asia, 5-9% in Europe, 13% in North America and 20% in Saudi Arabia [25].

Etiology of nephrolithiasis is multifactorial and can be caused by several different underlying diseases and numerous genetic conditions (hypercalciuria, gout and cystinuria) [26], and environmental factors including global warming [4, 27].

Weight, body mass index [28, 29] and diabetes mellitus [30] also increase the incidence of kidney stones; these last two are part of the metabolic syndrome affecting many populations at different levels of the healthcare system. Other diseases with increased risk of stone development are hyperparathyroidism, nephrocalcinosis, polycystic kidney disease (PKD), conditions with increased levels of vitamin D, sarcoidosis, spinal cord injury, and neurogenic bladder conditions. Gastrointestinal diseases (all intestinal bypass surgery, intestinal resection, Crohn's disease, malabsorptive conditions (including enteric hyperoxaluria after urinary diversion)) and bariatric surgery are also risk factors. [20]

Dietary risk factors are mainly associated with increased sodium and animal protein intake. Geographically, stone disease is more common in the developed western world and ethnically more common in white Caucasians than in Blacks [25]. The following text addresses some of the risk factors for stone disease.

Analysis of stone composition

A stone analysis should be performed in all patients and can be reconsidered in recurrent cases [20, 31]. To know what the stone contains is fundamental in medical stone prevention and treatment. It can also be of value in the choice of surgical treatment. Macroscopic or microscopic examination gives a rough perception of the stone's composition. Calcium oxalate/phosphate stones are smaller, colors vary, but they are always hard. Uric acid stones are yellowish. Struvite stones are off-white

or brownish and “soft”. Cysteine stones sometimes vary in color from yellow to green.

Infrared spectroscopy (IRS) or X-ray diffraction (XRD) or photomicroscopy are mostly used nowadays to determine stone composition. Chemical analysis (wet chemistry) is an alternative but is obsolete in Sweden. Other ways to determine stone constitutes are polarization, optical crystallography, MR spectrometry and chromatography [32].

Calcium

Hypercalciuria is present in 25–60% of stone formers [33]. The most common cause is idiopathic hypercalciuria. It is often familial and is strongly influenced by diet. Patients typically have excessive intestinal calcium absorption. They may also have a decrease in renal calcium reabsorption, and sometimes also a decreased in bone mineralization. This has a link to calcium metabolism and to an excessive number of receptors for vitamin D. There is evidence that chromosome 2 is involved, with genes increasing the intestinal absorption of calcium [34]. Unusual and rarely seen explanations are: primary hyperparathyroidism, granulomatous diseases, primarily sarcoidosis, Vitamin D intoxication, milk-alkali syndrome, and overuse of carbonic acid inhibitors.

Phosphate

Phosphaturia in subjects with stone disease is under investigation. The function still remains somewhat unclear. Hyperphosphaturia might be a predictor of recurrent stone disease. [35, 36].

Oxalate

Hyperoxaluria is noted among patients with recurrent calcium stones. Most of the oxalate is produced by the body itself, and intake has little effect on its metabolism. But there is increased oxalate absorption in the gut from foods high in oxalate (nuts and chocolate etc.) or its precursors occurs as well. Intestinal disorders or bowel resection (including gastric bypass surgery and Crohn's disease) are common causes.[37-39].

Uric acid

Stones made of uric acid exist in up to 20% of the stone cases. Excess uric acid in the urine can also promote the formation of both calcium oxalate and calcium phosphate stones. High protein intake can also increase the formation of calcium

stones (reducing the solubility of calcium oxalate) [40-42]. Clinically this is usually associated with low urine volume and low pH in the urine. One clinical condition associated with uric acid stones is cancer in patients treated with cytostatic drugs (cancer-cell death causing "purine overload") [43].

Struvite/Infection stones

Pure struvite or Mg $NH_4PO_4.6H_2O$, is sometimes referred to as triple phosphate and contains no calcium. Struvite stones are formed when urinary bacteria (such as *Proteus*) produce ammonium ions as well as alkaline urine. Phosphate is present in its trivalent form, combining with three cations (normally ammonium, magnesium, and calcium). A common mixture is composed of pure struvite (Mg $NH_4PO_4.6H_2O$) and calcium phosphate (Ca_{10} PO_4 $6.CO_3$) [3]. Women are more prone to struvite stones than men [44], because of an increased prevalence of urinary tract infection (UTI).

Cystine

These stones are a result from an excess of urinary cystine. This is caused by a genetic defect in reabsorption of cystine in the kidney. Cystine is relatively insoluble in aqueous solutions such as urine. Cystine excretion can therefore easily exceed the upper limit of its solubility, unless the urine is diluted deliberately to reduce the concentration. These patients need to drink lots of fluid. Sodium restriction can also significantly decrease urine cystine excretion. It is an uncommon autosomal recessive disorder [45]. Cystine stones are visible on plain radiographs, and well visible on CT-KUB. These patients are diagnosed at a young age in Sweden.

Drug induced

Some drugs cause kidney stone disease. The model drug, serving as an example, is the HIV medication Indinavir®. It creates stones that are hard to detect, both on plain X-ray and on CT-KUB [46].

Glycoproteins

The effects of the few proteins and glycosaminoglycans that pass through the kidney into the urine are complex. Some are found in the stone matrix, specifically, osteopontin/uropontin, Tamm-Horsfall protein, urinary prothrombin fragment 1 and some subunits of the serum inter-α-inhibitor. It is unclear whether they act as attachment sites—hence promoters—when expressed on the surface of cells or as inhibitors of stone formation[3].

What promotes stone formation?

Hereditary aspects

The genetic influence on stone formation in idiopathic stone formers is considerable and twin studies estimate a heritability of >45% for nephrolithiasis and >50% for hypercalciuria. The prevalence of monogenic kidney stone disorders, including renal tubular acidosis (RTA), primary hyperoxaluria and cystinuria, is approximately 15% [47]. The effect of race on stone disease is very difficult to answer due to confounders, but prevalence and incidence rates are highest for whites, followed by Hispanics, Blacks, and Asians [4]. Hereditary diseases associated with stone disease are cystinuria (type A, B and AB), primary hyperoxaluria (PH), renal tubular acidosis (RTA) type I, 2,8-Dihydroxyadeninuria, xanthinuria, Lesch-Nyhan syndrome, and cystic fibrosis.

Food

When discussing food intake as a risk factor or cause of stones it is usually due to "excessive intake", i.e. not normal consumption.

Proteins can lead to hypercalciuria, hyperuricosuria and hypocitraturia (recommendation 0.8-1g/kg/day, a limited intake, and not what would satisfy those trying to develop their muscles, such as bodybuilders).

Salt is often enjoyed in food but can increase the calcium excretion in urine and at the same time reduce urinary citrate levels (recommendation 3-5g/day).

The intake of oxalate, which is found in spinach, rhubarb, nuts, and chocolate etc., is low in the Nordic countries but more common in the Mediterranean region. People with the rare condition of enteric hyperoxaluria should be counselled by a dietician to keep their intake at a minimum.

As always, the best foods to consume are vegetables, fruit, full grain bread, less fat and - if using fats these should be of vegetable origin [48]. Unfortunately. few live up to these standards.

High C-vitamin intake seems to increase the risk of stone disease in men but not in women [49].

Low urine volume

Whatever the type of stone, low urine volume is often one of the problems. Patients with stones have a lower 24-h urine volume than average [50]. Low urine volume is very frequent in stone formers, i.e. it occurs in up to 77% of people with kidney

stones [51, 52]. With urine volumes of less than 2 liters/day, the supersaturation of urine (calcium and oxalate) increases and sometimes in an exponential manner [53].

Low urine pH

Low pH can be a problem - it may lead to both uric acid and calcium oxalate stones [26].

Low pH has little practical effect on cystine stones, as the solubility of this substance remains minimal at most urinary pH values. But cystinuria leads to having a lifelong kidney stones, and treatments include increasing the pH value (pH > 7.5) [54].

Other conditions with acidic urine are medullary sponge kidney, hyperparathyroidism, carbonic anhydrase deficiency or use of carbonic anhydrase inhibitors, and in hereditary and acquired forms of renal tubular acidosis [55, 56].

Hypocitraturia

This condition occurs in 30–40% of stone formers, but with great variation.

RTA (renal tubular acidosis) and chronic diarrhea syndromes are rare but known causes of hypocitraturia. Dietary intake affecting citrate level in the urine is more common. Fruit content in the diet seems to matter, with more fruit being a good thing.

Hypocitraturia as an isolated abnormality is not common among stone formers but seen together with other defects such as hypercalciuria and hyperoxaluria. Hypocitraturia may also be related to high protein diets [57-59].

What limits stone formation?

Urine volume

The recommendation is to drink more than before and drink a lot!

Fluid intake should be as evenly distributed over all 24 hours as possible. A rough rule is to drink more than 2.5l/24h. This should result in urine levels exceeding 2 liters/24 h. A simple rule to all, is to take an extra glass of water at each break or meal. The difficult part is obviously drinking in the night. Water is usually the best fluid to drink. If juice is preferred, lime juice is best (as it increases citrate in the urine). Orange juice does the same, but it also increases the level of oxalate in the

urine which is unfavorable. Apple juice, unfortunately, only increases oxalate levels.

Coca-Cola is a bad choice as phosphoric acid reduces citrate levels in the urine.

Whether beer/alcohol is god or bad is unclear. Increased fluid intake is a good thing, however alcohol induces dehydration and affects ADH (Antidiuretic Hormone) which are unfavorable. Beer/alcohol also contains purines increasing urate levels in urine.

Medication and other substances/molecules

Hydrochloro-thiazide: A diuretic drug medication used for increasing urine volume. A normal dose is 25 mg twice a day. With this drug there is often a need for extra potassium administration as well.

Allopurinol: Inhibition of xanthine oxidase lowering the levels of uric acid in blood and urine. Normal dosage is 100 to 300 mg daily.

Alkaline citrate: Potassium citrate should be preferred over sodium citrate. Sodium increases urinary calcium excretion, thereby limiting the beneficial effect of the urine citrate. Citrate can work as an inhibitor of stone formation. The main effect being that it binds to calcium molecules in urine preventing calcium from binding to oxalate or phosphate [60-63]. Alkaline citrates also increase urine pH which in many cases is beneficial. Normal dosage is 9-12 g per day.

Sodium bicarbonate: Alkalinization of urine. Used most for uric acid stones and cystine stones[64]. Dosage is normally 1.5 g three times a day.

Calcium: Taken orally tablet form, calcium reduces the uptake of oxalate in enteric oxaluria. These patients normally have calcium oxalate stones [53]. In cases of hyperoxaluria (excretion of >0.5 mmol/day and no excess calcium excretion) 500 mg per day at meals can be used.

Magnesium: Inhibits growth and aggregation of calcium phosphate stones. However, magnesium supplementation for stone prevention in humans has had disappointing results [65]. In cases of hypomagnesiuria, 200-400 mg daily is recommended.

Pyrophosphate: A naturally occurring substance in urine, pyrophosphate has been shown to inhibit both calcium oxalate and calcium phosphate crystallization [66-68].

L-Methionin: Makes the urine more acidic and has an effect on infectious stones [69]. If urine pH is constantly >6.2, medication with 200-500 mg three times daily can be used and the infection of course should be treated with antibiotics.

Pyridoxine (vitamin B6): Reduces hyperoxaluria, and is used for calcium oxalate stones [70]. High dosage ≈40 mg per day seems to reduce stone formation in women [71].

Tiopronin: Makes cystine more soluble in the urine. Used for cystinuria patients. When starting on 250 mg/day increase this by 1-2 g/day [72].

Coffee: Caffeine increases urinary excretion of calcium, sodium and magnesium. It also has a diuretic action if consumption exceeds 300-360 mg (4 cups of coffee/day). Coffee might have potential protective effects against the formation of urinary stones [73].

Tea: Exerts many protective effects against stone formation, through the accompanying water intake, the action of caffeine and the effects of components with antioxidant properties [74].

Phytate: Forms during maturation of plant seeds and grains and is a common constituent of plant-derived foods. The action of phytate as an inhibitor takes place both in the intrapapillary tissue and in urine [6, 75].

Osteopontin/uropontin: Inhibits spontaneous nucleation as well as growth as shown under experimental conditions[14]. *Tamm-Horsfall protein, or uromodulin,* is a kidney-specific protein. It is made by cells of the thick ascending limbs of the Henle loop. It coats the luminal side of the epithelium and is the most abundant of the urinary proteins under normal circumstances. Its excretion rate is approximately 100 mg/day. [76]. It has not been demonstrated to affect nucleation or growth of most stones, but it has a powerful effect of inhibiting crystal formation. *Urinary prothrombin fragment 1*- Is produced by thrombin cleavage of the serum protein. It is an effective inhibitor of both calcium oxalate crystal growth and aggregation [77].

Lifestyle factors relating to stone formation

Both *coffee and tea (especially green tea)* seems to have a protective effect against urinary stones [73, 74]. *Physical activity* studies are inconclusive. Activity could reduce the risk of stone disease due to its effect on calcium metabolism and bone mineralization. Activities for longer periods of time causing dehydration, like when running a marathon, might however increase the risk of stone formation [78-81]. *Alcohol*: some effects are positive and some negative; and it seems to have no overall effect on the risk of kidney stone disease [78, 82]. Whether s*moking* is a risk factor for stones is also unclear and studies again are inconclusive [78]. It seems like sexual activity increases the stone free rate after ESWL but whether it affects the risk of stone disease remains to be investigated [83]. Probiotics containing oxalobacter formigens seem to reduce the risk of stone disease [84].The *metabolic syndrome* (including obesity, hypertension, high triglyceride levels, and diabetes) has proven to be a risk factor for urological stone disease [85]. As the increased risks

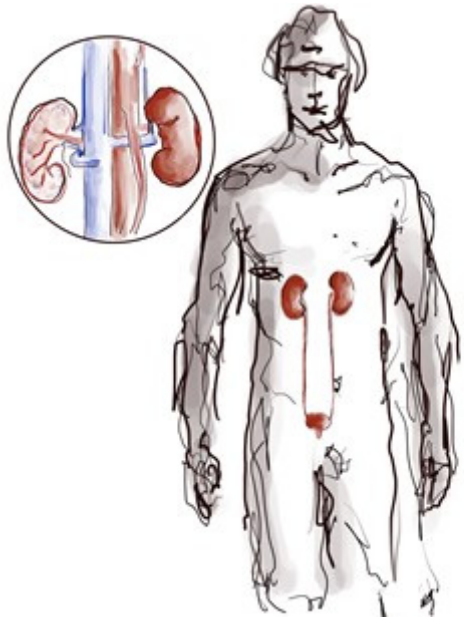
of stone disease seems most strongly associated with the metabolic syndrome, one could argue that an increase in physical activity and a reduction of alcohol and smoking would be beneficial at a population level. High ambient temperature has an effect and increases the risk of stones. Exposure to high doses of lead or cadmium also increase the risk of kidney stone disease [20]. Reducing salt and animal protein in the food and increasing vegetables and fruit in the diet are beneficial for many reasons including reducing the risk of stone disease [48, 84, 86, 87].

Natural passage of the stone

The natural passage of the stone through the urinary system is a subject of utmost importance in this field, but studies reflecting these data are scarce. The total amount of kidney stones that passes naturally is impossible to calculate, so estimations made from statistical analysis of smaller groups are usually made. The total figure for spontaneous stone passage is likely to be between 64% and 80% [88, 89]. The location of the stone matters for the probability of stone passage. Distal/lower stones clear at a higher rate than the proximal/upper stones. The ESWL study in this thesis also show this fact. The overall stone disease progression for asymptomatically found kidney stones, defined by the development of stone-related symptoms or stone growth, occurs in up to 80% of cases. Spontaneous stone passage occurs in 15% (more likely in stones <5 mm). The risk of surgical intervention for initially asymptomatic renal stones is approximately 10% to 20% at 3 to 4 years after discovery [3]. Below in the table is an estimate of stone passage probability [88].

Table 1. Stone passage rate at 4 weeks and 20 weeks, depending on stone width, measured in a standardized bone window (n=numbers and %).

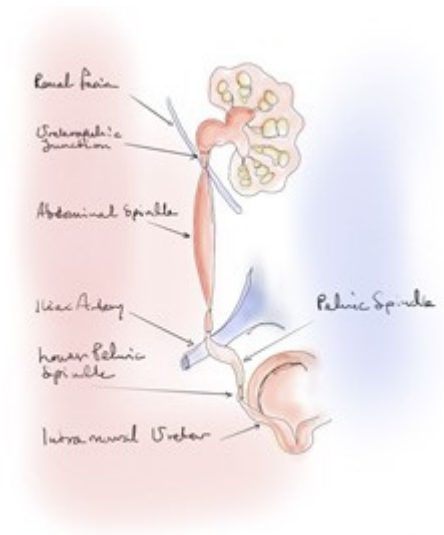
Stone size in mm (n/%)	Total after 4 w	Total after 20 w	Lower stones 4 w	Lower stones 20 w	Upper stones 4 w	Upper stones 20 w
<2.4(n=84/21%)	98%	98%	98%	97%	100%	100%
2.5-3.4 (n=121/31%)	92%	98%	93%	99%	87%	96%
3.5-4.4 (n=83/21%)	71%	81%	74%	83%	67%	78%
4.5-5.4 (n=48/12%)	47%	65%	68%	89%	9%	30%
5.5-6.4 (n=33/8%)	21%	33%	38%	57%	0%	16%
>6.5 (n=23/6%)	29%	9%	67%	33%	0%	0%
All stones (n=392)	76%	80%	84%	91%	52%	53%



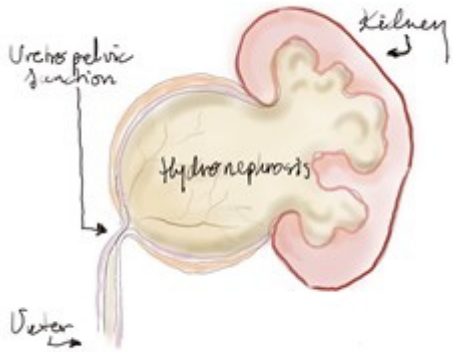
Anatomy and some physiology

The kidney is situated just below the diaphragm which is really high in the abdominal cavity [3]. It is protected by the ribs, the thoracic cavity and the back/spine muscles. Looking at the kidney from the front of the body, everything is "in front" of it [90]. This constitutes a problem when performing transabdominal surgery on this organ. Surgeons need to move almost everything, gut, colon, etc. to get to it. It has a "cap", the adrenal gland, which is important endocrinologically, producing cortisol, adrenalin etc. As it is one of the waste gauges, excreting urine, the kidney has a direct connection to the aorta and cava vessels and has an enormous throughput of blood. The cleaning process, filtrating blood through the kidney, is driven by pressure. There needs to be a pressure difference and this difference, the filtration pressure (normally around 20 mm/Hg), is what makes the process possible. It is affected by blood pressure and also by the pressure on the other side: the "urine pressure". A deeper understanding of this pressure difference might be available. Blood pressure has two phases: the systolic phase, around 140 mmHg, and the diastolic phase, around 80 mmHg. The capillary pressure in the kidney is around 60 mmHg and this is the arterial pressure entering the Bowman capsule. Plasma (blood fluid without the cells) has an oncotic "counter pressure" of around 25 mmHg and the other fluid "counter pressure" of the Bowman capsule is around 15 mmHg. This leaves us with a filtration pressure of around 20 mmHg [90]. Blood is pressed through the glomeruli (working like the crude separator driven by the difference in

pressure) filtrating about 180 liters of primary urine every day. The complex nature of the kidney parenchyma, including the “loop of Henle” concentrating and reabsorbing water and salts and then producing about 1.5 liters of urine a day, is one of nature’s chemical miracles. The volume corresponds somewhat to the weight of a person. When discussing patients in the ICU (Intensive Care Unit), a rough estimate of well hydrated people is indicated by urine production that corresponds in ml/h to their weight in kg (70 kg person producing 70 ml/h urine). The concentrated urine, leaving the loop of Henle, drops down through the papillae formed like inverted pyramids, into the renal calyces. Pressure in the renal pelvis is low, between 2 and 6 mmHg. The urine is drained quite rapidly down to the renal pelvis, and thereafter rhythmically pressed down into the proximal ureter. This process should not take too long in order to minimize the risk of stone formation as described earlier.



The first obstacle, or the place where some stones get stuck: the PUJ (Pelvi- Ureteric Junction). This is also a critical point where anomalies may arise. It is likely that some of these obstructions has developed prenatally. Changes in the ureter wall at PUJ can be seen. Sometimes the ureter is connected higher up in the pelvis, making draining suboptimal, as described by the Swede Karl Östling in his thesis in 1942 (sometimes referred to as “Östling kidney” or “Östling phenomenon”). Östling´s findings are not commonly referred to outside of Sweden and most consider this phenomenon to be a secondary effect of the expanding renal pelvis and gravity. Swedish urologists still use his name to describe this phenomenon and it needs to be addressed.



Another common cause of obstruction is a crossing/overriding vessel, usually an artery to the lower pole of the kidney, “nicking” the ureter.

The ureter works much like the gut, squeezing the urine (through peristaltic movement) aided by gravity down towards the bladder. The contraction wave of the propulsion starts in some cells in the upper calices, triggered by an increase in pressure within the renal pelvis. The depolarization wave propagates from one cell to another (as it does also in the heart and the sinoatrial node). It has a frequency of around 10/minute, emptying the system every 6-10 seconds with a small urine bolus (≈0.1ml) arriving in the bladder [90].

The next tight passage is when the ureter, sliding down behind all other organs in the retroperitoneal space, is pushed forward by the need to pass in front of the vessels providing and draining blood to and from the leg. Stones are easily stuck here and it is always a challenge to treat stones in this area endoluminally with an ureteroscope. Another surgical aspect of this “crossing” is that if surgeons have difficulty in finding the ureter during surgery, this is where to start looking.

The final tight passage is when the ureter is passing through the bladder wall. This passage is ingenious and works as a reflux mechanism (passing the wall tangentially, the bladder wall-tension prevents urine reflux) but unfortunately stones get stuck here as well. Another important fact about the ureter is that its wall is really thin proximally and “thicker” and more muscular distally, meaning that the risk of perforation increases proximally when performing endoscopy. Patients with calyceal diverticulum or cysts have increased risk of forming stones in the cyst. Urine is retained and crystallization occurs more easily. Ureteral stricture, vesico-uretero- reflux, horseshoe kidney and ureterocele are also more prone to stone formation probably due to the same reason, as urine excretion is prolonged [3].

Important development making stone surgery possible

When performing surgery, anesthesia is needed. Ether anesthesia was first described by Crawford Long in 1942. The discovery of “nitrous oxide” in 1945 was made by Horace Wells. Both of these discoveries are fundamental to the development of surgery.

The possibility of treating post-surgical infections comes with the discovery of “Penicillin” by Alexander Fleming in 1928 and the “Sulfa drug” in 1935 by Gerhard Domagk. Surgery leapt forward through handling postoperative infections. In Sweden one of the first “stone cases” we can read about is in the year 1889. The famous Swedish surgeon John Berg, through a vesicovaginal incision, extracted a distal ureteric stone. The patient survived and recovered without complications (like a fistula or infection), which to a modern surgeon seems like “pure luck”[91].

In the beginning of the 1900s, X-ray was introduced leading to the visualization of obstructing stones. The surgical approach at that time was normally a lumbar incision, taking an extraperitoneal approach to mobilizing the kidney and with the hand “feeling” the position of the stone, thereafter surgically removing it. It was big surgery with large incisions which was done at great risk to patients (first and foremost due to the risk of postoperative infections). The patient was usually admitted for several weeks, and in some cases months. The use of X-ray increased dramatically as a diagnostic tool and somewhat reduced the extent of surgical exploration.

In the 1920s Intravenous pyelography (IVP) was introduced. Knowing where the stone was situated using IVP, a German surgeon developed a “stone basket”. His name was Ludwig Zeiss, and the method was named “zeissning” in Sweden. This method, which used a small steel basket which was introduced up through the ureter “catching” the stone and extracting it by pulling it down into the bladder, had its shortcomings. It is often the case (if not always) that the stone is stuck for a reason (e.g. the stone is too big or the ureter too narrow), and when pulling to extract the stone, there is an immanent risk of ripping the ureter. With the basket and stone method, the distal ripped ureter in such cases resulted in large reconstructive surgery and great suffering for the patient.

The need to see what was actually going on became more and more pressing. Soon the development of the “ureteroscope” began. There is obviously no straight line from the urethral orifice to the kidney pelvis. The challenges of having a partly flexible instrument, producing light at the sight of the stone and presenting a correct view, were not easy to overcome. It was not until 1980 that the ureteroscope became a clinically useful instrument which was widely applied [3].

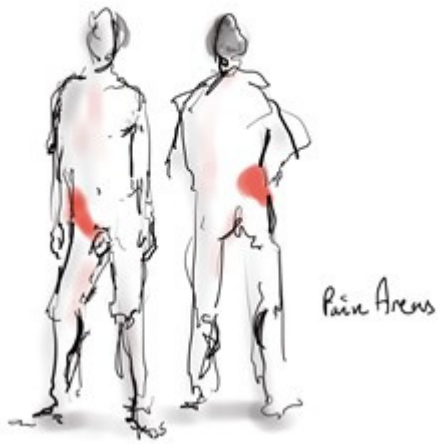
Stone surgery in the kidney pelvis was an open procedure until the 1970s when Fernström introduced minimal invasive percutaneous nephrolithotomy (PCNL) in 1976 [92]. In the 1980s extracorporeal shockwave lithotripsy (ESWL) was developed; this technique which crushes the stone within the body revolutionized stone treatment. When in 1985 electrohydraulic lithotripsy was introduced it commercialized the invention and made it useable for larger groups of patients. In the 1990s, more precisely 1993, the Holmium laser arrived: finally, a laser that could treat “all stones” was available

Radiologic evaluation/imaging

Non-contrast-enhanced computed tomography (NCCT) has become the standard for diagnosing acute flank pain and has replaced intravenous urography (IVU) [93]. The method has been refined with low dosage protocols and is usually referred to as computer tomography-kidney, ureter, bladder (CT-KUB). Review studies have shown that low-dose CT diagnosed urolithiasis with a sensitivity of 93.1% (95% CI: 91.5-94.4) and a specificity of 96.6% (95% CI: 95.1-97.7%), and if stones are >3mm, detects all stones [94, 95]. Ultrasound is used for children and pregnant women. Ultrasound is limited by a strongly reduced sensitivity (sensitivity of 45% and specificity of 94% for ureteral stones and a sensitivity of 45% and specificity of 88% for renal stones) [96]. Magnetic resonance imaging (MRI) is also an option for these two groups. NCCT presents the stone size in all dimensions, its density (measured in Hounsfield Units/HU sometimes also referred to as mean attenuation value/MAV), the skin-to-stone distance and surrounding anatomy. Cases in which size >10-11 mm, MAV values >900-1000 HU and SSD >9-10 cm seem to correlate with less successful treatment/SFR after ESWL [97-103]. The modern CT protocol is standardized in Sweden using 120 kV and 3/1.5 mm (slice thickness and interval) [104]. Measurements on stone size can be done in different "window settings" on the computer. The most correct way might be adjusting the "window level" to half of the measured stone density. "Soft tissue settings" will overestimate the size of the stone by ≈1mm (blooming effect), using the "skeletal window" will lead to an underestimation of the stone size by the same (≈1mm). When measuring density (HU/MAV) and using the "region of interest" (ROI), measurement should include 2/3 of the stone to avoid partial volume effects. HU values below 570 HU (or if a larger stone than 5 mm 750 HU) indicate uric acid stones, but infectious stones and cystine stones can also have values in this range. Dual-energy CT can be used to give us more information on stone composition, by identifies uric acid stones with good precision [105]. SSD is normally calculated from the skin at 0° (back side), 45° and 90° using radiographic calipers [106, 107]. The straightest way from the skin to stone, and the way ESWL is practically performed, is from the back avoiding the transversal extensions from the vertebra straight to the stone. We explored this way to measure SSD in paper IV. Many would argue that it is of great importance to get the information available from NCCT as soon as possible to guide the doctor in making the right treatment decisions. If stones are absent, the cause of the acute abdominal pain might be identified from NCCT, avoiding dangerous differential

diagnoses. Immediate imaging for stone disease is mandatory with fever or solitary kidney, and when diagnosis is doubtful [20].

Adding an intravenous contrast medium, CT urography (CTU), can provide additional information about renal function, the anatomy of the collecting system, and the level of an obstruction, and allows for rapid 3D reconstruction. This facilitates the planning of more complex stone surgery (used both in the workup of many URS and most PCNL cases) resulting in easier access and shorter operating times [93, 108]. A final comment on this topic is that obesity is a challenge for all investigative methods.



Symptoms

The pain is intense in a way that is difficult to describe for those who have not themselves experienced it. It can case vegetative symptoms, nausea and vomiting. The pain is often intermittent, i.e. “it comes and goes”; however, it may be more correct to describe intense and less intense periods, as some level of pain is often present. What causes the pain is an increased pressure in the renal pelvis (caused by obstruction of the urinary flow, usually in the ureter). An ultrasound of the kidney showing hydronephrosis can be expected if the patient is in pain. The pressure fluctuates somewhat due to the rhythmic squeezing of the system but also due to how much fluid actually passes the stone. The pain is described as “flank pain” following the level of visceral pain (the deep indescribable sensation from the inner organs) that is projected in the corresponding peripheral nervous dermatome (Th 11-L1). On the effected side, the pain extends from the spine over the lower ribcage and then radiates anteriorly and downwards. Distal stones sometimes get mistaken for appendicitis or ovarian torsion etc. and pain can radiate down and be projected in the genitals or thighs. Stones lying in the kidney pelvis rarely cause any pain but may do so if they are obstructing a calyx or calyceal group. These free stones in the renal pelvis are however often highly mobile, and when bigger than 6 mm they are considered to be a risk for later causing obstruction on their way out. Calcifications in the parenchyma of the kidney is usually not associated with pain. Calcifications in the parenchyma can be associated with other kidney diseases or seen as a rest of a healed condition such as bleeding or infection. Microscopic hematuria is quite commonly seen in stone disease, and macroscopic hematuria is more rare [109-111].

Basic laboratory analysis

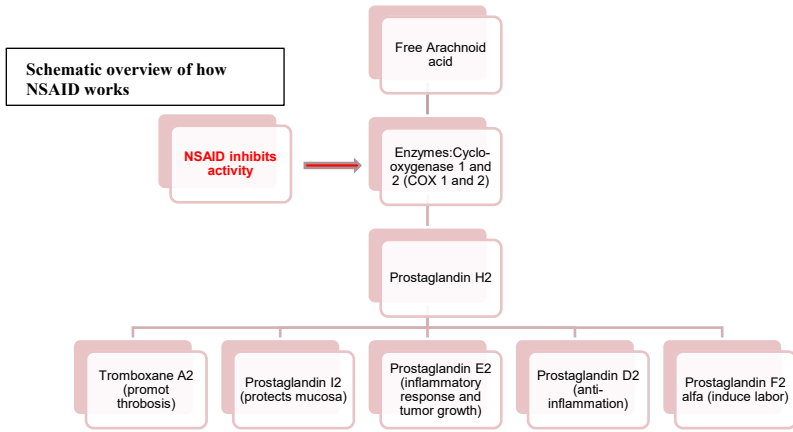
The following discussion will address the basic laboratory evaluation of the stone patient, leaving out the more thorough medical investigation and urine analysis sometimes needed in stone patients. A urine sample with a “dip-stick” is performed on most patients including red cells, white cells, nitrites and sometimes an approximation of urine pH-value. Microscopic hematuria strengthens the suspicion of stones [3]. White cells and nitrites indicate infection/inflammation. Most would also recommend a urine culture as bacteria could be one of the causes of stone disease and are treatable with antibiotics. The recommendation is to take a blood/serum sample including creatinine, uric acid, (ionized) calcium, sodium, potassium, blood cell count and C-reactive protein. Creatinine as an acute test is of limited use as it is elevated in almost all stone cases [20]. Increased levels of uric acid which indicate gout and increased levels of (ionized) calcium hyperparathyroidism are possible causes of stones. Sodium, potassium and blood cell count are routinely taken but their value is questioned if no surgery is planned. C-reactive protein is important, giving information on serious infection and usually affecting decisions regarding admittance and intervention. There is strong evidence that a stone analysis should be made if possible (see stone analysis). If surgery is planned a coagulation test should be performed (partial thromboplastin time and international normalized ratio). Comorbidities must be taken into consideration and testing in such cases be expanded. Pregnant women and children also require special consideration [20].

Treatment

Pain

Pain requires immediate treatment in the acute phase of a stone attack. In most patients renal colic is caused by ureteral stones. Extrinsic obstructions, such as junction pathologies and malformation, account for 10-15% [112].

Pain is caused by a pressure increase in the renal pelvis. This stresses the cells and triggers the release of prostaglandin E2 (PE2) and NO (Nitric oxide). Unfortunately, this leads to an increase in the blood flow of the kidney, increasing urine production and causing the pressure to rise even more. The effect of PE2 and NO will normally come to an end after ≈5 hours when the Renin-Angiotensin system will cause a vasoconstriction and reduce blood flow and urine production [3]. The optimal drug eliminates pain, preserves renal function and eliminates the obstruction. *Metamizole* is a drug not registered for humans in Sweden but used in Europe and in Sweden on animals. It blocks prostaglandin synthesis in the same way as *non-steroidal anti-inflammatory drugs (NSAIDs)* but also has a spasmolytic effect on smooth muscle. NSAIDs work by inhibiting prostaglandin synthesis, can be effective as a painkiller, and have an anti-inflammatory effect which reduces the swelling around the stone (enabling the urine to pass around the stone). NSAIDs also reduce blood flow to the kidney and thereby the glomerular filtration leading to a reduction in urine volume, thereby lowering intrarenal pressure. This last effect on the renal blood flow is potentially dangerous. It can cause ischemia and damage the kidney, and caution must be taken to avoid overdosing [113].



Opioid analgesics affect opioid receptors in all nerves including the brain. These work only as painkillers but are very effective and with trained personnel the risk of overdosing is minimal. However, the risk of patients developing a drug dependency (opioids induce euphoria) over time establishes a limitation for the use of drugs in this group. Alfentanil is an opioid with potent effect and short duration and is widely used in treatment situations (see ESWL).

Antidiuretic hormone (ADH) makes the urine extremely concentrated, keeping urine production at a very low level. Here there is the risk of fluid retention in the body. This can induce congestive heart failure and there is a risk of electrolytic changes that limit the use of this drug to a minimum (it can be more safely used in younger patients) [112].

In summary, NSAIDs, preferably diclofenac, are the drugs of choice for this condition with the following exceptions [113]. Opiates are the first-choice therapy during pregnancy (since they have no teratogenic potential and do not affect the blood supply to the fetus). *Paracetamol* (N-acetyl-p-aminophenol) is sometimes considered first treatment for pediatric use. It has none of the adverse side effects that are associated with NSAIDs or opioids. *Alfa blockers* (Tamsulosin) have been included among the drugs that are used for stone expulsion. The reason is that there is a high concentration of alpha-1D adrenergic receptors in the terminal ureter. Inhibition of the alpha-1D receptor might relax smooth muscle in the intramural ureteral tract, making it easier for both the stone and urine to pass [114].

Treatment indication

Apart from treating the intense pain, which is a very high priority for the patient, it is vital to realize that the high intra renal pressure caused by the obstruction actually damages the kidney and its function. This is what the pain signals.

The following section will clarify some physiological facts regarding urine production. As mentioned above, urine is produced due to a pressure difference of around 20mmHg called filtration pressure. Urine production can be affected by prerenal, renal and postrenal factors. Prerenal cause: if blood pressure is reduced less urine is produced. The simple way to explain this is by using the parallel of a major bleeding. Under such circumstances it is rational for the body to try to "save" all the rest of the fluids, and no or very little urine will be produced. Renal cause: the kidney itself is affected by a malaise (infection etc.,). Postrenal cause: an obstructing stone, and also urinary retention, causing the counter pressure to rise (less filtration/urine produced) [3].

Oliguria (sparse production) is the term when less than 400-500ml urine/24 h is produced. *Anuria* applies to less than 100-200ml/24h in the adult.

As humans normally have two kidneys and stones usually only affect one side at a time, the obstruction from a stone is "compensated" by production from the other kidney and the urine volume is only slightly affected. But high pressure slowly damages the affected kidney. If urinary flow has been totally obstructed for one week, ones the obstruction is removed the kidney will recover fully. After 2 weeks only 70% of function will remain, after 4 weeks 30% and after 6 weeks the kidney will be irreversibly damaged and left without practical function [115]. In real life the obstruction is rarely absolute and the time to severe damage is longer.

The old study on dogs from 1956 was the origin of defining follow up recommendations and guidelines (usually a follow up X-ray is recommended within 3-4 weeks) but it also point out that delaying treatment in some cases causes irreversible kidney damage.

The body also uses the flow of urine as protection against the invasion of bacteria, by continually "flushing" bacteria out; therefore, an obstruction to urinary flow may increase the risk of infection. An important fact that also needs to be considered when discussing treatment of these patients is that the combination of an obstruction and a bacterial infection above the stone is a life-threatening condition. It demands immediate action in order to avoid sepsis and death of the patient. See section on infection [116, 117]. Kidney stones with infection eventually always cause a problem for the patient and these stones need treatment. Patients with a solitary kidney need special consideration. Having one kidney itself does not particularly increase the risk of stone formation, but prevention of stone and recurrence is of more importance. Early onset of urolithiasis, especially in children and teenagers with a long life ahead and a stronger association to hereditary or familial stone formation, often requires multidisciplinary caretaking.

What affects the choice of treatment?

Treatment and the choice of method is always a discussion between the doctor and the patient. Doctors have to consider all aspects of the obstructing stone and the patient's abilities/disabilities. The *size* of the stone: if smaller than around 6mm in diameter, doctors should definitely give the stone (and the patient) the chance of passing the stone by natural means. If the stone is much bigger, i.e. "enormous", and/or if the kidney function is very low, nephrectomy might still in modern days be the best option. Everything in between >6mm and "enormous with impaired function" can be regarded as a treatment indicator needing further consideration [3]. The treatment recommendations referred to below is in line with the EAU Guidelines [20].

Location: If larger than 6 mm and situated in the *renal pelvis or high in the ureter,* most people – especially patients – tend to choose and prefer ESWL as the first treatment choice.

When treating stones with ESWL all the fragments "remain in the body" and need to be passed the natural way. Stones bigger than 1 cm create a lot of smaller fragments. If they are many and the patient is "unlucky" the risk of complications (as that of "Steinstrasse") increases. This could be overcome by the placement of a double-J catheter or nephrostomy (draining the urine regardless of the stone). Both have their drawbacks and cause discomfort for patients. If *the stone is really large,* above 1.5 cm (it rarely happens outside of the renal pelvis), PCNL is the best and quickest method of getting rid of the stone.

URS is not at all uncomplicated and the method has a medium risk of complications as described below under surgery (some are very troublesome, such as strictures). The ureter wall is thicker in its distal parts, reducing the risk of penetration/serious damage, and the distal ureter is usually quite easily accessible. This is why URS is considered as the first treatment option for most *distal stones* larger than 6mm.

Type of stone: Doctors rarely initially know what type of stone they are treating. With recidivating stone formers, you may have a qualified guess regarding stone type. Methods are developing that make knowing "ahead" possible, like the dual-energy CT scans which now, with good accuracy, can identify ureteric acid stones. In Sweden most patients with cystinuria are diagnosed in their youth and this will be known to both the nephrologist and the urologist. The type of stone can have an effect on the choice of treatment, but still any treatment can be used. Nowadays most clinics have a Holmium laser which means "any" stone is treatable; this was not the case with some of the older laser types.

Other treatment indications/aspects: This is more complex and should be carefully evaluated before treatment. *Pain* occurs in rare cases when the stone is in the renal

pelvis. It happens when the stone intermittently obstructs a calyceal neck or sometimes by the same action in a cyst.

Intermittent *bleeding* may be due to intercurrent bleeding disorders or be associated with antithrombotic treatment but can also be caused by stones or cancer. Macroscopic bleeding in the urine should always be promptly investigated and cancer excluded. Bleeding caused by a stone can be a treatment indication if it leads to anemia or reduced quality of life. Recurrent *infections* may also be a treatment indication, where the source of infection is believed to be the stone; this usually requires a selective culture from the upper urethral system on the effected side. Intercurrent morbidity and other illnesses, anatomical considerations and anomalies must be considered and evaluated. Not treating asymptomatic stones, usually lower calyceal stones in the renal pelvis, is acceptable. The decision not to treat and to evaluate stone growth using CT-KUB after six months and thereafter yearly depending on age and patient preferences can be recommended for asymptomatic, and normally smaller stones.

But still, the most important factor when deciding the right treatment is a well and adequately informed patient who is reflecting and participating in the choice of stone treatment and which modality to use.

Medical expulsive therapy (MET)

Medical treatment, facilitating the stone to pass, needs also to be shortly addressed.

All MET treatments are based on increasing the urine volume to “flush” the stone out and relax (dilate) the ureter with medication which facilitates natural passing of the stone [20].

MET is an alternative if the patient’s preference is “nonsurgical” treatment. The treatment is disputed and guidelines on the subject have changed in clinical practice during recent years. The greatest benefit of MET seems to be among patients with > 5 mm ureteral stones and preferably those with distal stones. Alfa receptor blockers have an effect in “relaxing” the ureteral wall. The distal ureter has a lot of alfa receptors as described earlier. Phosphodiesteras-5 inhibitors (PDE-5 inhibitors like sildenafil /Viagra®) work through inhibiting c-GMP and also relaxing smooth muscle, and corticosteroids being “anti-inflammatory agents” have been suggested to render an additive effect with α-blockers. These data are not yet consistent [118].

Chemolysis

Percutaneous chemolysis can be an option for infectious and uric acid stones, but due to practical reasons, that it is very time consuming and requires a nephrostomy, is nowadays rarely performed. In Sweden Renacidin® (Citric Acid, Glucono delta-lactone, and Magnesium Carbonate) [119] have been used for this; THAM solution has also been used [120]. Complications arise if there is an increase in intrapelvic pressure. Risk of sepsis and hypermagnesemia (rare and with diffuse symptoms) may then occur [20].

Oral chemolysis, usually by alkalinization of the urine with intake of sodium bicarbonate or alkaline citrate, are recommended for uric acid stones. Doctors must note the risk of hypercalciuria and the risk of calcium stones developing by alkalinization [20]. The practical results are somewhat disappointing [119].

Guide wires

The lifeline of all stone surgery is a guide safety wire. Guidewires function in many different ways [121] including helping to obtain safe access to the upper urinary tract by threading catheters and endoscopes on/over them. They “straighten” the ureter, bypass strictures and let surgeons “back out” in a safe controlled way, sometimes aiding the placement of a stent after the procedure. They can be characterized by their length, size, tip or their resistance to kinking. The most used guide wire is the 0.035 in (2.7 F) nitinol, coted (practically impossible to kink) with PFTE (hydrophilic polymer, polytetrafluoroethylene) stiff guide wire with a straight but soft/floppy tip [3]. The problem with these guide wires is that they are extremely slippery when handling, and that they need to be kept straight (they are not easy to handle when looping). When performing PCNL most surgeons choose a guide wire that is less prone to slip out, twined nitinol like the Lunderquist® wire [122] is a good example. “Backloading” the flexible ureteroscopes wires needs to be longer and have floppy tips at both ends to avoid damaging the working channel of the expensive ureteroscopes.

Catheters

There is need for urine drainage in the case of obstruction. The development of catheters began as early as 3.000 B.C. Nowadays a “bladder catheter” is a hollow tube with an inflatable balloon keeping it in place in the bladder. If obstruction of urine is persistent it will lead to organ damage, life-threatening infection or even

death. In old literature there is evidence that in China they used onion stalks and that the Greeks and Romans used tubes of wood or precious metals to drain urine. The word “catheter” originates from a Greek verb meaning "let down" (dropping or maybe “dripping” the urine). Benjamin Franklin , one of the Founding Fathers of the United States, invented silver catheters for his brother John. The catheter holes differ according to their use (for example, Couvelaire or Whistle tip for gross hematuria). The male urethra is S-curved and a dangerous passage is the sphincter-plane and the prostate. To facilitate this passage the Coudé tip catheters were developed in the 18th and 19th centuries. Nowadays there are many different tips. The mostly used “special tip” is the Thieman tip which is a modern form of the Coudé tip. The rubber catheters were developed in the 1860 (Nélaton), but these were soft at body temperature, with the lumen collapsing, and drainage was therefore suboptimal. The first self- retaining catheters had wing tips (Malecot) or flexible shoulders (Pezzer) [3].

Rubber vulcanization changed this (Goodyear, the tier manufacturer, invented this in 1844) by making the catheter firm and durable. Latex rubber arrived in the 1930s. The Foley catheter was developed by Dr. Frederic Foley and he introduced the “latex balloon catheter” in 1935. Catheters today without a balloon are usually called “Nélaton” and the ones with a balloon are called “Foley” catheters [123].

The balloon was initially intended for creating pressure at the TURP (Trans Urethral Resection of the Prostate) site with a hemostatic function, and it is still sometimes used for this purpose as well. Its main function today is to act as a simple and ingenious device for keeping the catheter safe in the bladder without too much discomfort for the patient.

The modern disposable catheter was developed by David S. Sheridan, the “Catheter King”, in the 1940s. Nowadays there exist different styles (different holes and different tips) and materials (silicone rubber, nitinol, nylon, polyurethane, PETE latex, and thermoplastic elastomers) for catheterization. The silicone catheters are the most commonly used, they are inert and do not react to body or medical fluids [124-126].

When urologists discuss the size of catheters they talk of “thickness” or diameter. The thicker the “better drainage” but, of course, also the more discomfort for the patient. This was first described by a Frenchman named Charrière (Ch). He measured the circumference in millimetres (3mm=3Ch). The tale told (but not true, I guess) is that the Americans had great difficulty in pronouncing Charrièr so they just called it “French”. The French scale (F/Fr) or French gauge (Fg) system is nowadays also used to measure the size of a catheter. Gauge is a measurement of needles or tubes, the Birmingham gauge system. French is 3 times the diameter of a circular catheter, and with 3 being almost the same as π (3.14) one can say that these two measures are about the same. (For those who have forgotten old school math, the circumference of a circle equals π times the diameter.)

Obstruction of the upper urinary tract exists as well, leading to the development of catheters bypassing strictures or stones in this area. To make these catheters hold their position creative engineering has led to the development of the "pig's tail". These catheters are introduced in the ureter or renal pelvis over a stiff guidewire in a straight manner. When the guidewire is extracted the end of the catheter is "curled up" like a "pig's tail", making the catheter hold its position. They are also called double-J catheters and are widely used in urology. They work as an inside catheter between the kidney and bladder passing the obstruction, for example, caused by a stone [127]. The advantage of being "inside the body" does not mean that the patient does not feel the sensation of its placement. Placing it with a cystoscope causes pain, and analgesics, sedation or anaesthesia are needed. When in place it can cause bleeding, there is the risk of infection rapidly arising from the bladder to the kidney and, when micturating, urine will reflux to the kidney pelvis causing pain like a limited stone attack. Some patients tolerate this well, others think it is "hell on earth". The single J catheter is not often used, it has a pigtail end in the renal pelvis but has an open end in the other side, going out through the urethra. However, its use is increasing due to the limitations of applying a nephrostomy catheter when patients are receiving anticoagulant therapies. It also facilitates evaluation of urine production, by taking samples etc. The nephrostomy, a catheter from the pelvis of the kidney directly out through the skin in the flank, is mostly undertaken by a radiologist under ultrasound guidance. The nephrostomy has its advantages: it can be applied even on a total stop in the ureter and it is easily changeable if there is a problem. Nephrostomy enables evaluation of the kidney's separate function, taking samples, and "flushing" debris, and it provides an opportunity for antegrade pyelograms. When a nephrostomy is applied the pressure in the renal pelvis becomes low or even pressureless. Even if it causes discomfort to the patient it is important if there is a life-threatening infection, cancer in the ureter or if the life expectancy of the patient is short (<6 months). The limitations of conducting a nephrostomy are first and foremost related to the risk of bleeding, as mentioned above. Bleeding disorders are quite rare. But nowadays many patients receive anticoagulation treatment for other medical conditions.

Infections and stone

This thesis addresses infection in adults, as infection in children requires a different approach. I will discuss infections of adult in an overview manner. Even if hematogenic infectious spread occurs I will leave this out. Infections of the bladder are referred to as "cystitis" and infection of the upper urinary tract, often including the kidney, is referred to as "pyelonephritis". The bacteria need to enter the system through the meatus of the urethra, defying the mucosa, being able to resist he constant flow of acid urine trying to flush out the bacteria and battling the other

parts of the immune systems in order to make the urinary infection emerge. Even so this occurs quite frequently. Females have urethras less than half the length of males and are therefore more prone to infections. The "bacterium of bacteria" in the urinary system is *Escherichia Coli*. It is a Gram-negative, facultative anaerobic, rod-shaped, coliform bacterium of the genus *Escherichia* that is commonly found in the lower intestine of the gut (most urinary tract infections originate from gut or skin bacteria). This is the most common cause of urinary tract infection, and many other bacteria exist (for example, *Enterococcus Faecalis* – a gram-positive, commensal bacterium also inhabiting the human gastrointestinal tracts) but we can use E.coli as an example. If there is a reflux of urine from the bladder to the ureter (like with a double J-catheter) the risk of a high infection "pyelonephritis" exists [3]. As the mucosa is defensive for all types of intrusion, bacteria like to "hang on to" foreign bodies (like catheters) or to stones and appreciate if the "urine flushing" is reduced, as in cases where there is a stricture. Most urinary tract infections can be easily managed by antibiotic treatment. When performing urological surgery, the bacterial spectrum is more diversified than in the normal population and surgeons need to know what type of bacteria to treat; a urine culture is essential. Nowadays bacteria are developing more resistance to all antibiotics, so we also need a measurement of bacterial resistance, again culture is needed. Prophylactic antibiotics as a single dose or as time-limited doses which reduce complications have been scientifically studied [20, 128] and are used in many surgical procedures, also in urology. If there is an ongoing urinary tract infection, we treat it or postpone the surgery. A special case is when there is an infection above an obstacle (like a stone). This can cause a "suspended pyelitis", a life-threatening condition that needs to be dealt with promptly. Especially dangerous is the combination of increased pressure in the pelvis/kidney and bacteria/immune response hitting the kidney and body. The condition is septic due to the infected "abscess" and pus retained under pressure in the kidney pelvis. Intensive and immediate treatment including intravenous broad-spectrum antibiotics, fluids, monitoring of vital functions, sometimes in the Intensive Care Unit/ICU and, maybe most importantly, drainage [129, 130] need to be performed. It is, however, not scientifically proven to be better than using a double J-catheter than a nephrostomy [117, 131]. But if surgeons choose to use the double J-catheter as drainage, they will have to anesthetize the patient, which is more expensive, it will prolong the hospital stay, increase the use of analgesics and the patient will suffer from fever longer than if undertaking a nephrostomy [132]. Emphysematous Pyelonephritis is a rare condition not uncommonly associated with diabetes mellitus and sometimes with stones and can require acute nephrectomy [133]. In stone treatment with ESWL among the older population, an increased risk of asymptomatic bacteriuria exists. Patients who have received an indwelling urethral catheter, nephrostomy or double J-catheter are at risk of having bacteriuria. It seems probable, that the risk of infectious complications from urological stone surgery is increased when parts of the catheter are exposed outside the body (nephrostomy, bladder catheter), but this remains to be scientifically proven.

Crushing the stone may lead to bacterial exposure in combination with trauma from the ESWL/URS or PCNL mixing blood and bacteria – possible sepsis is the worst case scenario [134]. A commonly used classification system that grades infection and sepsis is the SOFA score; an example is shown below.

Table 2. The Sequential Organ Failure Assessment (SOFA) Score: a score ≥7 on initial evaluation is associated with significant shock, with a score ≥13 associated with significant risk for mortality in the intensive care setting (MAP=Mean arterial blood pressure mmHg and vasoactive agents administered for at least 1 hour).

SOFA score	1	2	3	4
PaO^2/FIO^2(mmHg) **Or SaO^2/FIO^2**	<400 221-301	<300 142-220	<220 67-141	<100 <67
Platlets x $10^3/mm^3$	<150	<100	<50	<20
Bilirubin (Micromol/L)	20-32	33-101	102-204	>204
Hypotension	MAP<70	dopamine ≤5 or dobutamine	dopamine >5 or noradrenalin ≤0,1	dopamine >15 or noradrenaline >0,1
Gascow Coma Score	13-14	10-12	6-9	<6
Creatinine (micromole/L or Urine output(Ml/day)	110-170	171-299	300-440 <500	>400 <200

Stone disintegration

As described earlier, open surgery was one of the first methods used by doctors to remove stones. The endoscopic way came later. Retrieving stones with a basket "Zeissing", also mentioned before, has its shortcomings. Manually crushing the stone with a stone-grasper specially made for this, usually called a "Punch" in Sweden, works well when applied to stones in the bladder but works poorly in the ureter and renal pelvis. This is mainly because these instruments are small, and the power exerted through the instrument is usually not effective enough to crush the stone [3]. "Crushing methods" for stones that work endoscopically in the upper ureter tract are electrohydraulic (EHL), ultrasonic, ballistic and laser lithotripsy. EHL came in the late 1950s. With high voltage (around 5kV) the spark at the tip of the instrument creates a cavitation bubble crushing the stone. It is effective with crushing rates of up to 90%. To my knowledge it is not used in Sweden today, probably because there is a major risk of tissue damage with this method. But the same method (EHL) was also used to create ESWL shockwaves. In the 1980s

Extracorporeal shock wave lithotripsy (ESWL) was introduced and commercialized [135].

Ultrasonic lithotripsy developed in the 1950s. Electrical energy is converted into a sonic wave using hollow (or solid) metal rods making the tip oscillate at around 20Hz. The use of hollow metal rods with suction in the hollow part is quite satisfactory. In Sweden this is used for most PCNL procedures, sometimes combined with a ballistic lithotripter. It is effective in around 90% of stone cases, and with the addition of the ballistic part works fast and well without damage to the tissue in most cases. The ballistic lithotripter works like a miniature "jack hammer" driven by air under pressure (usually 3ATM and with a frequency of 12-15Hz) which is noisy but effective [136].

LASER

Laser is Light Amplification by the Stimulated Emission of Radiation. We know from "Star Wars" that it is created when energy is used to activate atoms of a medium like Holmium. The light atoms bounce between mirrors and at a certain wavelength they are allowed to pass through a "filter" and then enter a thin fiber. With this fiber the energy can be directed on to the stone in a pulsating manner. The first clinical laser was the "Pulsed-dye laser". It came into use in the 1980s and the wavelength was 504nm. It caused no tissue damage but failed to crush some stone types adequately. The "Holmium" laser (yttrium-aluminum-garnet) uses a wavelength of 2150nm and works on practically all stones. The laser can cause tissue damage which can be useful cauterize bleeding and does so when in contact with tissue [3]. There are many other lasers too many to discuss here. Regarding fiber technology it is worth mentioning that the thickness/diameter of the fiber limits the amount of energy (measured in Joules x Hertz/Hz) that can be directed at the stone. The semirigid scopes usually use around 300um and the flexible ones around 200um. Other important aspects are the frequency or Hz and long or short pulsing of the laser. You can choose if you only want to crack the stone, to chop pieces off it (short pulse, Joules higher around 10 and 1 Hz) or to make really small fragment "dusting" (long pulse, Joules low <0.5, high Hz 40). The dusting technique requires more powerful and more expensive laser machinery and can be problematic with harder stones [137]. The latest laser, the thulium fiber laser, has come into clinical use. It can break kidney stones into pieces that are 10 times smaller than with a holmium laser. Producing smaller particles makes it easier to leave fragments as small as possible and will probably have an effect on SFR [138].

ESWL (Extracorporeal Shock Wave Lithotripsy)

In aviation, hypersonic flight means a challenge for the resilience of the airplane structure. Rain drops create a shockwave destroying the material of the airplanes when flying really fast.

To mimic this experimentally, a shockwave machine was created in the end of the 1960s. Shockwaves cause no visible injuries when passing through muscle tissue, fat tissue or fascia but seem to have great effect in areas with high acoustic impedance, such as kidney stones. The Dornier HM1 (Human Model 1) – the first clinical lithotripter – was constructed, and the method was put into clinical practice[139] . In the 1980s extracorporeal shock wave lithotripsy (ESWL) was introduced and revolutionized urolithiasis treatment [140]. All ESWL systems contain a shockwave generator, a localization system (X-ray or ultrasound) and a positioning system (to move the patient and focus on the stone). The generator of the shockwave can be electrohydraulic, piezoelectric or, as most modern machines, electromagnetic. The generator is positioned in a bowl of steel reflecting the shockwave into a focal point. It is extremely important to maintain the energy of the pulse and water is usually preferred as the medium. Air reducing the effect of the shockwave immensely must be avoided. In the first models described above the whole body was in water "taking a bath" during treatment [141].

When performing ESWL you try to get as much energy as possible to "hit" the stone and thereby crush it. Modern machines allow the patient to have some water at the treatment site making treatment easier and more feasible by avoiding a bath for every patient. The electromagnetically produced shockwave is made in a steel bowl filled with water. To explain this in a simple way, think of it as a can of cola containing an electric coil. When applying electric current through the coil a magnetic field occurs, and since the current is alternating the can expands or implodes depending on the magnetic field. This is happening at a very high speed, creating sound waves bouncing on the steel-bowl walls aimed at a point above the "focus point". The energy or the effect of such waves will, as with any other wave, lose power with distance and be affected by the medium it moves through. The shockwave is short in time, at around 4 microseconds. The pressure wave rises quickly reaching up to 40 Mpa and is followed by negative pressure replacing it being as low as -10 Mpa at the focal zone. These pressure differences are what make the stone crack [3]. There are at least four stone breaking effects. The *Hopkinson effect*, hitting the stone in the back due to a reflection effect, *shear forces*, *squeezing effect* and *cavitation* [3]. These phenomena also affect all tissue and, of course, the kidney but at a much lower level. Still there are situations when ESWL should not be performed. Contraindications usually recognised are pregnancy, untreated coagulation abnormalities, most anticoagulants, tumours or aneurysms in the shockwave path, active/untreated pyelonephritis and untreated high blood-pressure [142].

ESWL is an effective treatment [143] and has gained worldwide acceptance. It is today considered to be the first line treatment for more than 75% of patients with urolithiasis. It is also cost effective [144]. The development and introduction of different shock wave sources, coupling and imaging techniques have improved both treatment, comfort and results.

The need for anaesthesia has vanished and with good pain reducing drugs and modern machinery ESWL is performed at an outpatient clinic.

ESWL is well tolerated, even by the sick and elderly [145]. However, the optimal device remains to be found for lithotripsy which will provide high efficacy with no need for anesthesia and with minimal tissue trauma. For the time being, ESWL in Sweden remains the first-line treatment for stones between 6-15mm located in the upper third of the ureter and in the renal pelvis [135]. Many use alfentanil, an opioid with short duration for treatment of pain during the therapy, at a dose of around 10ug/kg intravenously. The effect is very good, but short and rarely affects vital functions, such as breathing. It is important that the patient is comfortable during the treatment procedure, as anxiety or pain induces movement which makes urologists "miss" the stone. Increased breathing sometimes puts the lung and air in the way of treatment which is unfavourable. Merely normal breathing moves the kidney and the stone quite significantly, normally around 15mm and makes some of the shockwaves miss their target. Good pain relief and control are needed. Starting ESWL on a lower energy setting with stepwise power ramping, thereby achieving vasoconstriction has a protective effect on kidney parenchyma. Under good conditions stone-free rates reach up to 90% [3]. Although complete stone clearance in more complex cases is not always achieved by ESWL, relief of symptoms, reduced infection and saving kidney function may still motivate use of ESWL treatment [3].

A persistent challenge for urological surgeons treating stones with all modalities, is choosing the right treatment modality for the right patient; or maybe even more crucial, it is choosing what treatment not to recommend due to risk of complications or lack of effectiveness in that specific case. A limitation of ESWL treatment is that urologists have to "see" the stone on X-Ray or ultrasound and be able to focus the shockwave on the stone in three dimensions. Most use X-ray for focusing which requires that the stone is somewhat dense (maybe >450 HU) to make ESWL possible [146].

Urologists strive to select the best treatment and categorise the patients correctly. The risk that the stone contains bacteria always exists. Bacteria play a part in the formation and sometimes growth of the stone. Many patients treated with ESWL are elderly, making the risk of asymptomatic bacteria always something to consider. Many doctors use a quick-test/a dipstick to screening for bacteriuria. Some patients also have an indwelling urethral catheter, therefore at risk of having regular bouts

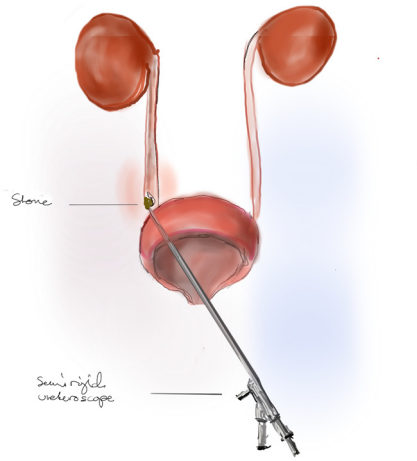
of bacteriuria. Sepsis, which is the worst case scenario in treatment-associated infections, occurs in 1-3% [134].

The size of the stone has an impact on treatment and the choice of method. When treating a larger stone it leaves us with the problem of "Steinstrasse": stone fragments "queuing up" in the ureter causing obstruction and pain which occurs in 4-7% [147]. Smaller and sometimes really small fragments can cause pain, obstruction and require surgical removal [148]. This is sometimes addressed by "stenting" using a double J-catheter or nephrostomy tube; these solutions are mostly considered for bigger stones, >1 cm. Another problem is regrowth of residual fragments which occurs in 19-59% [134]. ESWL has an effect on the tissue and an intrarenal hematoma is quite common (14-19%) but becomes symptomatic only in less than 1% [149]. Dysrhythmia or arrythmia is common and occurs in 11-59% [134] but has little clinical significance. The risk of other tissue damage has been reported as case reports, liver and spleen hematoma, perforation of bowel etc., but these cases are extremely rare.

Paper 1 describes side effects and complications of ESWL treatment.

The optimal treatment for kidney stones might be impossible to achieve. Most believe that better estimation regarding SFR could be reached by having more information about the stone. One stone measurement could be replaced by two or even three measures, providing stone volume which may be a better predictor of treatment effect and the risk of complications using ESWL.

A better understanding of the size may also provide guidance about the number of ESWL treatments needed, giving patients a better estimation of when treatment results might be obtained. An important factor in the treatment effect/results is also the distance from the skin to the stone (SSD). Living in the western world, people get more overweight each year and the SSD gets longer. The effect or energy hitting the stone is reduced by the distance, therefore making it more challenging to treat stones with ESWL. In Paper IV this is investigated as well as objective radiographic measurements that affect ESWL treatment.



URS (Ureteroscopy)

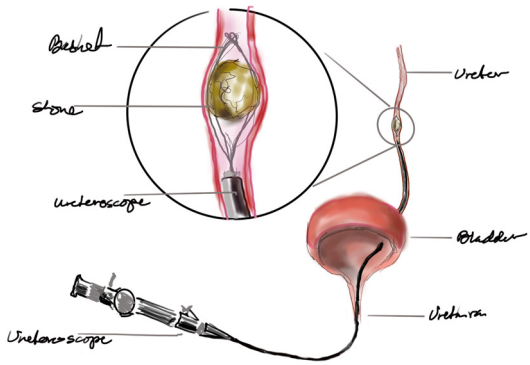
The idea of being able to investigate malaises through the body's natural orifices has been around forever. Initially "doctors" investigated blood, saliva, stool and urine samples to put forth a theory of the diagnosis and its origin (the theory of bodily fluids). This famous model consists of the four humors, first described by Hippocrates: black bile, yellow bile, phlegm, and blood with their corresponding four temperaments [1].

Investigation of the body and theories of its function existed through autopsies at an early stage. But looking into the living body was, and in some ways still is, limited. Pain needs to be controlled, there are aspects of ethics, challenging technical issues, and contamination etc.

The first ureteral tube that was used to inspect the urethra and the bladder was designed by Bozzini in 1806; the limited light came from a candle. Maximilian Nitze developed the first usable cystoscopy (Kystoscop) in the late 18th century and the beginning of the 19th century. Working with and grinding the optics and creating different angles made it possible to look at/inspect the sides/walls of the investigated organ (0-30 degrees are nowadays standard). The first endoscopes were extremely fragile, and any tension might make the lenses crack. The development of better optics made it possible to divide the glass rod into many smaller glass rods, allowing movement without cracking, leading to our "semirigid" scopes still in use today.

The problem with all older cystoscopes was first and foremost light. This was improved by the rod lenses (Hopkins), but the solution came as late as the 1960s with fibreoptics.

Further technical progress was achieved with the development of flexible scopes. Then they were made thinner, which enabled examination of the ureter to find and treat stones there [3].

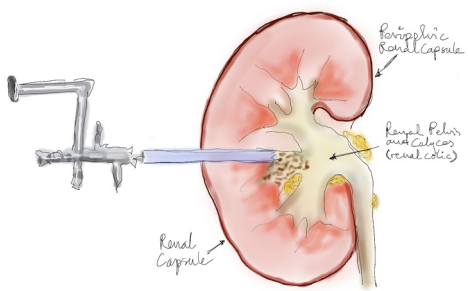


Nowadays the flexible ureteroscopes are very usable, with flexible angles from 0 to 270 degrees, thin (6 French), easy to handle, and digital with a “chip on the tip” sensor for producing the image [142]. The image is projected onto a large screen that can be adjusted to the surgeon’s comfort when performing surgery, also making tutoring a lot easier than previously. A flexible scope has many advantages. When performing a cystoscopy, which is done under local anaesthesia, surgeons can follow the s-shaped urethra with as little discomfort for the patient as possible. It also makes it possible to inspect and work at different angles. Still, today most distal ureteric stones are treated with semirigid ureteroscopes. This is because they are easily handled, durable and canulating the ureteric orifice is much easier than with a flexible scope. Normally no access sheets are needed and most urologists use the semirigid scope as their first-choice instrument for the distal ureter. Studies suggest that ureteroscopy (URS) is as effective as extracorporeal shockwave lithotripsy (ESWL) for treating stones including the ones in proximal parts of the urinary tract [150, 151]. The guidelines of the European Association of Urology (EAU) [20] recommend using either ESWL or URS for stones < 2 cm. With the exception of untreated urinary tract infection (UTI) and contraindications for general anaesthesia, URS can be safely performed in a majority of patients. The Holmium: YAG laser is effective for all types of stones and is nowadays considered the gold standard for stone disintegration. Preoperative stenting has been shown to facilitate URS treatment [152]. Postoperative stents in URS have a place in selected cases but cause irritative lower urinary symptoms when used [153].

Stone-Free Rate (SFR) is used to measure outcome and successful treatment. Residual stones ≤4 mm in diameter after treatment are considered clinically insignificant, and the patients considered stone-free [154]. The complication rates range from 9-25%, after URS [20]. A urine culture is mandatory according to most guidelines, and patients with a UTI should receive antibiotic treatment prior to URS [20]. The most common bacterium causing UTI is *Escherichia coli* [155]. The complication rates for post-URS UTI´s and the rates of sepsis range from 2% to 4% [156].

The second study retrospectively evaluated the outcome of patients treated with URS, additionally describing the complications related to this treatment. The discussion of whether stone surgery should be done outside normal working is debated within the urological community. The influence of personnel not specially trained in urological procedures, on call operating personnel and whether the surgeon's fatigue may affect outcomes and complication rates are some of the questions addressed in paper II.

Evaluating and understanding the complications may potentially lead to better patient selection and consequently improved safety for patients treated with URS.



PCNL (Percutaneous Nephrolithotomy)

The majority of stones greater than 6-7 mm require urological intervention [157]. Indications for active stone removal in the renal pelvis are symptomatic stones (pain, bleeding, infection) or stones affecting renal function. As stones greater than 6-7 mm are at risk of causing obstruction when passing the ureter and also cause

infection, these patients are normally considered for active treatment [20]. Open renal stone surgery is now rarely performed since the development of extracorporeal shock wave lithotripsy (ESWL), flexible ureteroscopy and percutaneous nephrolithotomy (PCNL) [158]. PCNL, first described by Fernström et al. in 1976 [92], is today the treatment of choice for patients with kidney stones greater than 1.5-2 cm, lower pole stones greater than 1-1.5 cm and staghorn stones. Staghorn calculi/coral calculi, are renal calculi obtaining their shape by forming a cast of the renal pelvis and calyces, thus resembling the horns of a stag [159]. Contra indications to performing PCNL are untreated UTI, potential malignant tumour in the kidney or in the way of accessing the renal pelvis and pregnancy. Known complications to PCNL are fever (2.8-32.1%), bleeding requiring transfusion (0-45%), organ injury (0-1.7%) and sepsis (0.3-1.5%) [160]. The Clavian classification system can be used to evaluate the morbidity associated with PCNL [161]. The EAU Guidelines recommend urinary culture and treatment of all bacteriuria preoperatively [20]. Positive stone culture and pelvic urine culture seem to be better predictors of urosepsis than midstream voided urine taken preoperatively [162].

To evaluate a patient before PCNL the patient should be well informed of the different treatment options and be fit enough for 3-4 hours of surgery. In the preoperative workup, a CT-scan with contrast focusing on the kidney is mandatory; sometimes the functional partition of the stone bearing kidney must be evaluated [20]. A renogram is medical imaging using an injected radioactive isotope and a Gamma camera investigating the function of the kidneys separately. An important organ to avoid when puncturing the renal pelvis is the colon. If the colon is in the way of the puncture line, puncture needs to be done under ultrasound r CT guidance. At the current time, the Guy's Stone Scoring (GSS) system [163], the STONE nephrolithometry scoring system[164], and the CROES (Clinical Research Office of Endourological Society) nomogram [165] are used for the prediction of the success rate and possible complications following PCNL in research and sometimes in clinical practice [166].

Table 3 (which can serve as an example of systems for pre-operative evaluation of stone/surgical complexity, and as a predictor for SFR). (≈success rate GSS1-90%, GSS2-70%, GSS3-50% and GSS4-40%)

Guy's stone score 1 (GSS1):	a solitary stone in the mid/and or lower pole or in the renal pelvis with a normal anatomy and simple collecting system
Guy's stone score 2 (GSS2):	a solitary stone in the upper pole; multiple stones in patients with simple anatomy; or a solitary stone in a patient with abnormal anatomy
Guy's stone score 3 (GSS3):	multiple stones in a patient with abnormal anatomy or in a calyceal diverticulum or partial staghorn calculus
Guy's stone score 4 (GSS4):	a complete staghorn calculus or any stone in a patient with spinal bifida or a spinal injury, calculus in patients with clinical neurological alternations (spinal cord injury, myelomeningocele)

Most surgeons place a thin ureteral catheter up and into the renal pelvis, sometimes with the possibility of inflating a balloon to avoid fragments from "falling down in the ureter" during the PCNL and securing postoperative drainage. It also presents the opportunity to introduce a contrast medium (usually with a blue dye/methylene blue) to the renal pelvis, making the puncture and introduction of the dilation instruments or balloon better and safer. The catheter is then tied to a normal urethral catheter which is cuffed in and which drains the bladder.

Thereafter most surgeons turn the patient to a prone position (face down). An alternative to the prone position is the supine one. There are several advantages to the supine method as anaesthesia is easier, and surgeons save time not having to reposition the patient. Studies also show that the risk of damaging the colon might be lower [142]. It also presents the opportunity to work on the stone both from the retrograde and antegrade direction without repositioning the patient. The drawback for most urologists is that they need to learn puncture with ultrasound guidance. In Sweden not many are familiar with the method and it is not often used. Using the "prone" technique a contrast medium (with a blue dye) is injected, dilating the renal pelvis which allows it to be punctured through a calyx with x-ray guidance. The limitation of the puncture triangle is medially the spine, below the crista Iliaca and above the 12 rib (it is possible to puncture above the 12^{th} rib safely [167]). The skin is a limitation to the later dilating process and the incision needs to be long and deep enough for this.

The puncture is the critical part: once surgeons have perforated the renal pelvis, contrast will start leaking, so they really need to be accurate. The angle and the depth are also challenging, demanding different X-ray angles during the puncture procedure. When rightly made, the puncture follows the blood vessels with practically no bleeding as a result, but with the wrong angle this could start a serious bleed, too deep that it hits even larger vessels [90, 142]. There are other ways of obtaining good and safe access: one is using a flexible ureteroscope puncturing from the inside out. When I trained to become a PCNL surgeon, we used stepwise dilators, but this is only used on rare occasions nowadays. Balloon dilation is fast safe and works fine for most stones [168]. How large does the hole into the kidney pelvis need to be? This is the subject of lots of discussion on PCNL technique in the last few years. Normally the dilation process is up to a sheet size of 24-30 French (F=3 times the diameter in mm), whereas the mini-PCNL sheet is 14-20 F. One could conclude that with the right selection of patients the mini-PCNL is as effective and safe, and may have less risk of complications compared with the normal PCNL method [169]. Stone disintegration in PCNL is done by ultrasonic lithotripsy combined with ballistic lithotripter and suction [136]. Laser and graspers are used when required. To make sure that all the accessible stone is removed and that no fragments have slid down in the ureter, a flexible thinner instrument is used for inspection and additional stone removal. Before finishing, most surgeons place a nephrostomy into the renal pelvis. To shorten the postoperative time and discomfort

of the patient one can choose to leave out the nephrostomy which is known as a "tube less procedure". This can be recommended if the bleeding is minimal, operation time short and if thinner instruments have been used. There are of course both pros and cons to "tubeless". The bladder and the ureteral catheters are normally extracted the day after surgery and an antegrade X-ray is done the next day. Contrast medium injected through the nephrostomy tube the next day, ensuring normal passage through the ureter to the bladder. Thereafter the nephrostomy can be removed, and the patient can go home.

Paper 3 evaluates the treatment results and complications of PCNL performed 2009-2015 at the stone centre in Ängelholm. The aim was to identify risk factors associated with postoperative infectious complications and to investigate the correlation between pathogens found in stone material and postoperative sepsis.

This third study completes the aim of describing a modern transection of stone surgery, examining all stone surgery performed in the north-western part of Skåne during the years 2009-2015 (Helsingborg/Ängelholm).

Complications

The most common complications of stone surgery are pain and infection, followed by organ injury (urethra, bladder, ureter or kidney) and bleeding [20]. Organ damage of the urethra or ureter usually heals with stenting but can result in strictures and may require reconstructive surgery. Sepsis is the most lethal risk of infection complications following stone surgery. Haemorrhage is rare with URS but occurs both with ESWL and PCNL. Stricture risk, especially with proximal and large stones, is not uncommon with URS. PCNL has dangerous, but rare complications; examples are organ perforation (mostly colon), urinary leakage, hydrothorax, pelvic perforation and urinary fistula [170]. Any symptoms after surgery, stenting or nephrostomy tube insertion/removal - such as flank pain, nausea, vomiting, or blood in the urine - should be promptly investigated with appropriate imaging to ensure that the kidney is not obstructed and clarify the cause of pain [20]. One important thing about complications is to be able to compare different workups, approaches, techniques instruments, drugs etc. "Common ground" regarding what to address as a complication and a grading system have been long needed. The Clavien-Dindo classification system gives us this opportunity. The study authors choose to report complications according to this system, as do many others nowadays [170, 171]. Smaller modification in regard to method (ESWL/URS/PCNL) must be made. Modified Clavien-Dindo classification from the ESWL article, Paper I, is presented below:

Table 4 The complications group according to Clavien-Dindo grade in the first ESWL study.

Variable	Number of patients(%)
Complications (Clavien-Dindo grade)	116 (6.3%)
Grade 1	
Fever	9 (0.5%)
Renal colic/Pain/Other causes	33 (1.8%)
Grade 2	
Pain (admitted not operated)	29 (1.6%)
Renal hematoma	6 (0.3%)
Grade 3a	
Obstruction (relieved by Percutaneous nephrostomy)	8 (0.4%)
Grade 3b	
Obstruction (relieved by JJ stenting)	15 (0.8%)
Steinstrasse (relieved by JJ stenting URS)	16 (0.9%)
Grade 4	
Urosepsis	7 (0.4%)

Aims of the thesis

The main focus of this thesis is urological stone treatment. The studies are clinical cohort studies focusing on treatment effects and complications of most surgical stone treatments. These studies, based on the three treatment alternatives, can be specified as follows: ESWL -Extracorporeal shockwave lithotripsy, URS - Ureteroscopy and PCNL - Percutaneous nephrolithotomy.

Complications in Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study, objective: To evaluate clinically relevant complications of ESWL in the northwest of Skåne in a modern setting.

Ureteroscopy: A study of clinical complications and possible risk factors for stone surgery - a population based study, objective: To describe the complications of URS and to investigate whether performing URS outside normal working hours leads to increased risk of clinically significant complications.

Percutaneous nephrolithotomy and modern aspects of complications and antibiotic treatment, objective: Describes complications of PCNL focusing on infections, bacterial growth/resistance and antibiotic prophylaxis/treatment.

Factors influencing stone free rate of Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study objective: To evaluate factors affecting SFR such as age, stone size, skin-to-stone distance and mean attenuation value/Hounsfield on ESWL treatment results.

Patients and methods

Papers I-III included all patients receiving stone surgery at the Urology Clinic in north-western Skåne County (Helsingborg/Ängelholm Hospital) between the years 2009 and 2015. Number of consecutive ESWL, URS and PCNL treatments between 2009 and 2015 were: ESWL n=1838, URS n=568, and PCNL n=186.

In paper IV we included all ESWL treatments in the same cohort/population between the years 2015 and 2019 (n=707).

Statistical analysis. Statistical analysis for details, see the articles. For investigating correlations between a binary variable and a non-binary variable, univariate logistic regression analyses were first used. If the analyses were found to be statistically significant, multivariate logistic regression analyses were used comparing multiple covariates to the same dependent variable. When multivariate logistic regression analysis was used, gender and age were included as predefined confounding variables when required. Bonferroni-correction was considered but not used. When comparing quantitative parameters, that were normally distributed, means were compared with t-test. If data were statistically skewed or samples were small, Mann-Whitney's test or Kruskal-Wallis test was used. P-values <0.05 were considered statistically significant. The statistical analyses of paper I-III were made using IBM SPSS for Mac OS v24.0.0.0. In paper IV all computations were performed in R: A Language and Environment for Statistical Computing version 4.0.2. All statistical work has been verified by a statistician.

Results

Paper I: Complications in Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study

From 2009 to 2015, 1169 patients received treatment in 1838 ESWL sessions. It is a large single center study of ESWL. Success rate with ESWL alone was high, 71.8% (n=1324). Stone location of treated stones were renal pelvis 64% (n=1185), upper 2/3 of ureter n=415 (22.5)% and lower 1/3 of ureter 11.1% (n=205). Single treatment was used most frequently 76.7% (n=1414). The most common complementary treatment was URS 14.4% (n=265) followed by expectancy/X-ray follow up 14.2% (n=261). Most patients did not receive antibiotics 61%(n=1116). Diabetes was present in 9.3% (n=170) of cases. The percentage of patients with stents (double-J or nephrostomy) was 24% (n=443). A total of 6.3% (n=116) of the patients sought medical attention within 14 days after ESWL treatment. Of the 116 patients who sought medical attention, microbiological agents were found in cultures in 33 cases. *Escherichia coli* was most common in 0.6% (n=11) of the cases. Of the 1838 ESWL treatments, admission for hospital care was needed in 4% (n=75) of the cases. The mean length of hospital stay was 2.4 (1-13) days. Overall, infection was found in 1.9% (n=36). Intravenous antibiotics were administered as treatment in 1.2% (n=22) of the treatment sessions. 2.4% (n=44) of patients sought medical attention due to symptoms of infection. The admission rate was 2% (n=36), and 7 of the patients had sepsis. Of the sepsis patients, none had an infection with a microbial agent resistant to the antibiotic given as prophylaxis prior to ESWL treatment. Stones sized 21-30 mm (p=0.012/OR=3.32) and diabetes (p=0.02/OR=2.10) increased the risk of complications. Of the 47 patients admitted due to non-infectious reasons, the main cause was obstructive pain and uropathy, and 2.2% (n=41) patients underwent an operation. An additional 1.3% (n=24) of the patients were admitted for various reasons such as hematuria, chest pain, stroke and various other non-urologic, non-infectious reasons.

The overall long-term mortality during the study period was recorded. All 1169 patients had a follow up time in terms of mortality of at least 1 year. Cases were inspected and none of the deaths was considered to be linked to ESWL treatment. Distal stones have a better stone free rate than more proximal stones and a lower risk of complications . The risk of complications after ESWL increases with stone size and if there was need for antiemetic drugs during ESWL treatment. Patients with diabetes have an increased risk of complications. The results indicate that there

is a lower risk of complications using 1Hz (compared to 1.5 Hz) when performing ESWL.

The study has significance in perioperative counselling of patients in need of ESWL treatment for their stones.

Paper II: Ureteroscopy: A study of clinical complications and possible risk factors for stone surgery - a population based study

Between January 2009 and December 2015, 486 individual patients were treated with URS in a total of 568 sessions. The overall SFR was 90.7% (n=515). In 60.4% (n=343) of cases the patients could be discharged from the hospital on the same day. If admitted the mean hospitalisation time was 2.0 days. 14.3% (n=81) required multiple sessions, where 4.9% (n=28) of the patients were treated two times, five patients were treated three times, and two patients were treated four times. 3.5% of patients (n=20) were re-treated for the same stone within 6 months. Age, sex, Charlson Comorbidity Index-score, diabetic comorbidity, long-term mortality, and the Clavien-Dindo classification score, stone location, stone size, and the use of ureteral stents were studied. All patients who were readmitted within 14 days were scored ≥1 according to the Clavien-Dindo system. SFR divided according to preoperative stone size showed a 100% success rate in stones ≤4 mm (n=112). SFR for stones was >4≤6 mm 96.2% (n=176), for stones >6≤10 mm 84.6% (n=193), and for >10 mm 68.2% (n=30). Of 20 patients re-treated for the same stone within 6 months, 20% of patients (n=4) had a residual stone size of ≤4 mm. This was 10.5% of all patients with residual stones, initially considered stone free.

When comparing SFR following operations by on-call OR (operating room) nursing staff/evening or night (SFR of 97.6%) with operations during normal working hours (SFR of 89%), also adjusting for age/gender, no significant difference was found. A positive urine culture was found in 15.9% of the patients (n=90). The most common pathogen was *Eschericha coli* 35.6% (n=32) and the second most common was *Enterococcus faecalis* 19% (n=17). A total of 14% (n=79) of the patients received preoperative antibiotic treatment, 60% (n=341) of patients received perioperative antibiotics, and 18% (n=103) received postoperative antibiotic treatment. Of the perioperative antibiotics, aminoglycoside was the most used type: 69% (n=235). Sixty patients, 10.6%, sought medical attention within 14 days, of these 67% were readmitted. The causes of readmission were infection 32% (n=19), pain 22% (n=13), bleeding 10% (n=6), and other causes 3% (n=2). Of the patients admitted, 20% (n=12) had a SOFA (Sequential sepsis-related organ failure assessment) score ≥2 and one patient was admitted to the ICU. Univariate logistic regression model was used with SFR, re-admission, SOFA score >2, or mortality as the dependent factor. The univariate logistic regression analyses showing statistical significance, p≤0.05, were further investigated in multivariate logistical regression, adding the predefined confounding variables of gender and age. SFR is significantly improved by stone location in the ureter (p<0.001, OR 0.515, CI 95% 0.389-0.682),

preoperative smaller stone size (p<0.001, OR 0.728, CI 95% 0.654-0.810), and no use of a postoperative ureteral stent (p=0.009, OR 0.418, CI 95% 0.217-0.804). Using readmission as the dependent variable, only Clavien-Dindo (p<0.001, OR 8.014, CI 95% 5.220-12.304) was confirmed to be significant. Mortality was not increased if the patient was re-admitted within 14 days. No significant differences were found for risk of surgical complications in regard to the time of day (0800-1700 vs other), ordinary vs on-call personnel, acute vs elective surgery and flexible vs semi rigid ureteroscope. Age, however, was significant in all groups and receiver operator curve (ROC) curve analysis was performed. Most accurate cut-off point of age, regarding age and the risk of complications, was 65 years (AUC 0.6).

Charlson Comorbidity index, preoperative stone size, and stone location in the ureter showed no statistically significant association with postoperative risk for complications (p=0.227, p=0.274, p=0.720, respectively). Univariate logistic regression analysis was performed with diabetes and Clavien-Dindo (dependent variable) showing no statistical significance (p=0.717).

Paper III: Percutaneous nephrolithotomy and modern aspects of complications and antibiotic treatment

A cohort study including all 186 patients undergoing PCNL, 2009-2015, at Ängelholm Hospital. Mini PCNL was not used. Stone free rate was 65.6% (n=122). Of the patients 1.6% (n=3) had a urethral catheter, 14.5% (n=27) had a double JJ-catheter and 11.8% (n=22) had a nephrostomy catheter preoperatively. Of all patients, 30.1% (n=56) had a positive urine culture preoperatively. The most common bacteria were *Enterococcus faecalis* (*E. faecalis*) and *Escherichia coli* (*E. coli*) with 19.6% (n=11) in both cases, followed by *Streptococcus agalactiae* 12.5% (n=7). Mixed flora was common 23.2% (n=13). One culture was positive for *E. coli* with carbapenemase production (carbapenem-hydrolyzing oxacillinase-48 (OXA-48)). Stone cultures were positive (>10^3 colony forming units/ml) in 33.3% (n=62). The most common bacteria reported were *E. faecalis* 25.8% (n=16) followed by coagulase-negative staphylococci 24.2% (n=15) and *E. coli* 16.1% (n=10). Both positive urine and stone cultures were found in 18.8% (n=35). The concordance rate between urine and stone cultures was 57.1% (n=20). 60% of these (n=12) also displayed the same resistance pattern. A positive urine culture increased the risk of complications. Of the 186 stones only 176 were available for analysis. For complex stones the combination of calcium, oxalate and phosphate were the most common, occurring in 58.5% (n=103). Calcium was detected in 92.0% (n=162), oxalate in 79.5% (n=140) and phosphate in 69.9% (n=123) of the stones. Other components analysed were ammonium, urate, magnesium, uric acid, struvite, carbonated apatite/trioxide and cysteine. Divided into groups, these were: calcium oxalate/phosphate 68%, infectious stones 19%, uric acid stones 9% and cystine stones 4%. All patients received antibiotic prophylaxis. The most common intravenous antibiotic was Cefotaxime 78% (n=145), followed by aminoglycosides

24.2% (n=45). Most patients received intravenous antibiotics preoperatively alone (83.3%, (n=155)). Patients with a positive culture received oral antibiotics followed by intravenous antibiotics in 13.4% (n=25). Additional postoperative antibiotics, after removal of the nephrostomy tube, were given to 48.9% (n=91) of the patients. Of these, Ciprofloxacin (500 mg x2 for 7 days) 47.3% (n=43) and Pivmecillinam (200 mg x 3 for 7 days) 25.3% (n=23) were the most commonly used antimicrobial agents. Of the patients with a positive urine culture, 44.6% (n=25) received oral antibiotics tailored to culture results and resistance pattern prior to admission, and the rest of the positive cultures were considered to have bacterial contamination. The patients receiving antibiotics prior to admission had a higher risk of developing any complications (p=0.008), but not sepsis (p=0.315), compared with those who did not receive per oral antibiotics. A total complication rate of 16.1% (n=30) was found in this study: 23 during hospital stay and 7 occurring within 30 days. Positive urinary culture or stone culture was associated with the development of any complication, p=0.017 and p=0.002 respectively.

No other possible risk-factors show any significant correlation with complications (age, sex, body mass index, stone composition, stone free rate (SFR), comorbidity, catheter use and mortality rate). Treatment of residual stones included: watchful waiting n=40, ESWL n=15, ureteroscopy n=8, and endoluminal antegrade approach n=1.

No significant association was found between serious postoperative infectious complications defined as sepsis and positive urinary or stone cultures. Of the sepsis patients 37.5% (3/8) had negative cultures from both urine and kidney stones. Only one patient had a positive blood culture (1/8), *E. coli* with ESBL-CARBA, in both urine and stone. Nearly all of the patients (5/6) who developed fever postoperatively received an extra dose of intravenous aminoglycoside (n=4) or carbapenem (n=1) followed by per oral antibiotics, normally for 7-10 days. Looking at all complications, 12.4% (n=23) suffered from one or more complications before being discharged from the hospital. Bleeding, defined as the patients receiving a transfusion, occurred in 5.4% (n=10), sepsis was diagnosed in 4.3% (n=8), fever episode in 3.2% (n=6), and reoperation in 1.6% (n=3).

Of all patients, 3.8% (n=7) sought medical care or required additional intervention within 30 days of being discharged. Of these, 5/7 had infectious complications, including 1 patient with abscess, 2 with pyelonephritis and 2 with urosepsis. One patient had haematuria and flank pain and one patient needed additional surgery (URS) due to a residual stone.

Long-term overall mortality, median follow-up (range 2 to 9 years) postoperatively, was 11.3% (n=21) none of these cases was related to PCNL surgery. Of these, 61.9% (n=13) were older than 70 years at the time of surgery and the majority, 90.5% (n=19), were diagnosed with at least one comorbidity. 52.4% (n=11) had a BMI of

25 or higher. No deaths were registered within three months of surgery. Median of hospital stay postoperatively was 3 days (ranging from 2 to 23 days).

The article is interesting, showing that *Enterococcus faecalis* is as common as *E.coli* in PCNL patients. This may have implications for antibiotic treatment and prophylaxis of this group. Even modern urological antibiotic guidelines for PCNL focus on treating *E.coli* not *E. Faecalis*. Another point with this third article (combined with paper I and II) is that together they are a presentation of all (but open surgery) surgical treatment options for urological stone treatment (in the same cohort and for the same time period).

Table 5 with results from article I-III

Treatment (patients/treatments)	**ESWL (1136/1838)**	**URS (486/568)**	**PCNL (186)**
Total complication rate (readmission rate) both in (%)	6.4% (4%)	10.6% (7%)	16% (3.8%)
Most common complication	Pain 4.4%	Infection 3.5%	Infection 11.3%
SFR	71.8%	90.1%	65.6%
Location Kidney	64.4%	10.2%	100%
Location Upper ureter	22.5%	17%	-
Location Lower ureter	11.1%	58.4%	
Urinary Tract Infection	3.3%	16%	30%
Double J-catheter	24.1% (Both JJ and Neph. included)	Before 15.9% , after treatment 34.9%	11.8%
Nephrostomy	24.1% (Both JJ and Neph. included)	-	14.5%
Urinary catheter	-	16.9%	1.6%

Paper IV: Factors influencing stone free rate of Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study

In this fourth article (not published yet) the aim is to try to optimize ESWL treatment results by improving selection of patients likely to benefit from ESWL. This study involved evaluating 707 of the 724 ESWL treatments between 2016 and 2019 in Ängelholm Hospital for stones <2cm. This study focuses on specific factors that might predict SFR/outcome of ESWL treatment. Objective factors known before treatment are, for example, age, stone size, skin-to-stone distance (SSD), hounsfield units (HU), stone location, and number of treatments. We evaluate factors affecting SFR.

We concluded that stone maximum size, stone volume and age, has an impact on stone free rate after ESWL. We are puzzled by age being such a strong predictor and this needs to be further investigated.

Table 6 with results from article IV:

Multivariate analysis of factors that could affect SFR after ESWL (HU and volume are odds ratios/100 units). Note that the effect of SSD disappears, possibly due to an association with size or age. Results are the same when taking into account max size instead of stone volume. (n=707)

Table 4	**OR**	**CI-lower**	**CI-upper**	**p-value**
Sex Male	1.253	0.78	2.014	0.352
Right side	1.322	0.815	2.142	0.258
Location Ureter	0.651	0.305	1.391	0.268
Pigtail stent	1.024	0.510	2.059	0.946
Nephrostomy	2.522	0.828	7.684	0.104
Age	0.944	0.928	0.961	**<0.001**
HU (100)	1.058	0.966	1.159	0.226
Volume (100)	0.940	0.908	0.973	**< 0.001**
SSD	0.974	0.874	1.085	0.634

Discussion and future perspectives

The general aim of the first 3 studies was to include all the stone surgery performed over five years in northwest Skåne. The first study evaluates clinically relevant complications to ESWL. Diabetes is mostly mentioned as a "late complication" in association with ESWL. In this study, we found a strong association between clinically significant complications and diabetes (p=0.02). Sugar leakage in the urine may contribute to a higher risk of infectious complications. The use of stents seems to have the same problem. To recommend general intravenous antibiotics to these groups (patients with stents and diabetes) might be taking it too far, but the following should be considered: optimizing diabetic treatment, ensuring a urine culture and considering antibiotic treatment for these groups. The bacteria we found in the cultures reflect our clinical experience of infections in urology, with 33% caused by *E. coli*. The increasing resistance in *E. coli* is an alarming fact and infectious complications in the future will be very challenging [172]. To use 1Hz when treating with ESWL is most probably better, reducing the risk of complications as shown in this article. Using 2Hz seems to reduce the effect of the ESWL treatment, so slower is probably the best way to proceed [20]. Antiemetic drug-treatment during ESWL correlated with increased risk of complications in this study. We have not anticipated this, but it seems logical that pain from tissue damage could cause a vagal response. The nausea might be a symptom of this vagal reaction but it is yet to be proven in further studies.

In the second study we tried to describe the complications of URS and investigate whether performing URS outside normal working hours increases the risk of clinically significant complications. The treatment results in this study with an SFR of 90% is comparable with other similar studies. Whether age is a factor that increases the risk of complications in URS is debated [173]. In our study we found that complications seem to increase with age and the ROC curve analysis indicates 65 years as a possible cut off age. This might be considered when planning URS in the future. Since the numbers in our study are small, larger studies are needed to confirm the results.

The third article concentrates on PCNL, describing complications with a focus on infections, bacterial growth/resistance and antibiotic prophylaxis/treatment. The stone free rate with PCNL was 66%, corresponding well with other studies and also reflecting the complexity of treating large and staghorn stones. It demonstrates the fact that complementary treatment is needed for some of these patients. The broad

spectrum antibiotics, such as the third-generation cephalosporins and carbapenems, should be used when there is a treatment indication only [20]. The standard perioperative drug recommended at our clinic at the time of our PCNL study was Cefotaxime, a third-generation cephalosporin. Aminoglycosides were the second most commonly used drug as additional intravenous therapy in our study. A general reflection is that none of these drugs is effective for *Enterococcus faecalis*. The large proportion of *E. faecalis* that we found in our study (20%) may change future antibiotic recommendations, given that these results are reproducible. Studies on urinary bacteria and their resistance will be needed at intervals in the future, to evaluate antibiotic prophylaxis in stone surgery (PCNL, URS and ESWL).

In the fourth article the aim was to try to optimize ESWL treatment results by improving selection of patients that are helped by ESWL. This study was impossible to conduct within the same time span as the previous three. There is a need for NCCT to assess objective parameters known before treatment, such as volume/max size, SSD, HU, location, number of treatments etc; NCCT was not performed routinely on all stone cases before 2015. The preliminary results show that age ($p<0.001$) and maximum size in mm/volume ($p<0.001$) have a significant impact on SFR. It is puzzling that age in this study is such a strong predictor of a successful treatment, measured as SFR. We have re-examined the figures and the result remain the same. It has been previously shown that age affects SFR [174]. It has been suggested that sclerotic changes in renal parenchyma occur with aging reducing the effect of ESWL on kidney stones. The effect seems to be the same with urethral stones so this might not be the only cause [174]. Long time SFR seems to level the difference of age, one explanation being that SFR takes longer with increasing age [174]. Our study is evaluated after 3 months and could be biased by this fact. But it be that other factors are affected by age and reflected in the age parameter in our study. Ageing normally reduces urine production, fluid intake, physical and sexual activity, elasticity of tissues and wound healing. A model containing age and volume seems to be the best way to predict SFR in this material. We present a simple model including age and stone size for an estimation of SFR after ESWL.

Methodological considerations

All studies in this thesis are observational in nature and are population-based cohort studies. In my doctoral plan the intention was that two RCTs should be included: one using a multi-centre method and both addressing aspects of drug treatment in research. I am still a part of these studies, but they are not included in this thesis. Evaluation-based on the input from the midterm external reviewers- led to the decision to include a fourth study focusing on stone treatment instead. It is my belief that the thesis as a whole has gained from this guidance.

This choice of direction, however, weakens the research methodology part of the thesis. It is well known that observational studies increase the risk of errors/bias. The selection bias in all three studies is obvious as all patients included were in need of surgical treatment for their stone disease. Other sources of selection bias affecting results could be waiting time affecting patient or doctor preference. Confounding bias can occur and age, as discussed above, could be such a factor. Information bias resulting from incorrect measurements is something that needs special consideration specially in paper IV. Being aware of sources of error, and discussing and working with these, are of great importance and we have tried to do so in this research. I also believe that our close cooperation with a statistician increases the reliability of the results.

Making this a stone thesis may be its greatest strength. The thesis includes 3299 surgical treatment sessions for urolithiasis. It is the largest number of stone treatments presented in a Swedish thesis as far as I know. It includes all surgical treatments during a 5-year period in the population of northwest Skåne. A urological thesis on stone treatment is exclusive in Sweden, as in the last 20 years only one has been presented (by Klas Lindqvist 2004). It is important that aspects of stone treatment are represented within the Swedish research community; hopefully this thesis will make a contribution in the stone field. Many patients are affected by stone disease both in our country and in the world, and further research of this group of patients is important. The material consists of a large number of patients and could be used for more studies on stone disease. There are many possibilities of future studies. Different aspects of costs related to stone disease could be one, the time from diagnosis until treatment or total treatment time for the different treatment modalities another. Relapse in stone disease and the risk of intervention and complications in the patients with residual fragments in a modern setting would be interesting to investigate.

General discussion

The aim in this general discussion is to address more structural issues that may be important for the improvement of urological stone treatment in the future. Patients receiving cancer diagnoses have shorter investigation workup and time to receive conclusive treatments. These improvements are driven by the “Standardized Care Procedures” (SVF in Swedish) [175]. Unfortunately, this has been at the cost of non-malignant diseases. Stone treatment is one of those conditions left with the opposite situation, namely fewer resources and longer time to surgery and cure. Stone surgeons believe that this prompts the movement of stone treatment in the same direction, by making an “SVF” for stone disease. The creation of Swedish national recommendations on stone treatment is in progress.

Urological stone disease is increasing, >50% in the last 10 years and this needs to be addressed. In Sweden we have chosen a conservative treatment policy for stone disease. In the Lindqvist et al study almost 20 years ago, they evaluated whether immediate investigation or deferred investigation of acute flank pain was better, using CT-KUB in the years 2001-2002 [176]. That study failed to show any real benefits of early investigation. The study has limitations, as it represented the Goteborg county, there were 172 persons that could be randomized and of those 150 could be evaluated. The study was conducted in the early stages of CT development, with time consuming and high dosage CT-KUB protocols. A study from Norway recently tried to address the same issue, but being small, retrospective and with a low response rate (48%), still leaves this issue unanswered [177]. Urological radiology has gone through drastic technical improvements in the last years. Radiation dosage for a CT-KUB has been sharply reduced, and control CT-KUB even more (≈1.5 mGy, absorbed dose≈ 0.7-08 mSv, this is a low dose) with maintained and sometimes even better results [178]. The question to answer is whether it is really true that stones pass spontaneously. The latest reviews on the subject conclude that 64% of patients passed their stones spontaneously (49% of upper ureteral stones, 58% of mid-ureteral stones, and 68% of distal ureteral stones). If the stone is small <5mm, almost 75% of stones passed spontaneously, suggesting that we need to know the size and location of the stone. The average time to stone expulsion is around 2.5 weeks and nearly 5% of patients required rehospitalization [89]. Early treatment is required as soon as possible, or at least within 48 h, and even seems superior using ESWL for some patients [179]. Knowing all this, is it still acceptable to hope that the stone will pass spontaneously? In Europe, the debate of "treating acute flank pain" has focused more on *how* to investigate this condition than on *when* and *if* to investigate. The high percentage of private urology clinics in Europe must be taken into consideration when reflecting on these recommendations (their feasible option being ultrasound). Ultrasound demands skilled personnel on site performing the investigation, which consumes time and resources. Ultrasound provides good data on kidney parenchyma and hydronephrosis, but limited knowledge of stone size and location [180]. Should ultrasound or CT-KUB be used as the investigative method? For most Swedish doctors and definitely for stone surgeons this question is easily answered. Most would never expose a patient to the risks of anesthesia and a surgical procedure if there "might be" a stone: this is the risk of performing surgery based on conclusions from an ultrasound. If you really need to know whether there is a stone or not, its size and location, you need to perform a CT-KUB. However, ultrasound should be used for pregnant women and younger children to avoid even low doses of radiation. Ultrasound could, if needed, be complemented with a CT-KUB in these two groups. The approach to take for the vast majority of patients with stone disease is CT-KUB using the new low dosage protocols.

A correct diagnosis with all the information received by a CT-KUB is the start of treating stone patients correctly. The exclusion of other acute and dangerous

abdominal pain conditions is of course also important; this occurs in around 10% of these cases [181]. In the group with acute flank pain 90% have a urological explanation for their pain, but only around 80% have a urethral stone as the cause of this pain. Of those, around 20% will require an emergency intervention [182]. You simply need to know what the problem is, or neither you nor the patient will be content. The correct diagnosis of stones gives us the early opportunity to suggest/discuss treatment options and present a time plan to the patient. Patients with larger proximal stones or increased risk of complications can be better prioritized, with optimized planning for further investigations and surgery. Patients with small stones might not even need any more X-ray investigations; it could be enough to provide a clinical follow-up. This follow-up can be performed by the General Practitioner (GP) or even better by a specialized "stone nurse", cutting radiation exposure, waiting time and costs. A training program needs to be developed and put into practice to involve nurses more and increase interest in stone care and treatment.

What is then the issue – why not just perform the CT-KUB? Costs and radiation exposure are what make most urologists hesitate. But will costs really increase? We actually do not know this for sure; many perform CT-KUB on these patients even today. Radiation exposure than? Maybe some patients will be unnecessary exposed, but if some of the stone patients will not need a follow up CT-KUB, it might even reduce total radiation exposure of the group. Small stones (<4mm) have an estimated stone clearance rate of 95% within 40 days [183] if the patient are without symptoms one might suggest that no more X-ray is needed. And again, the doses with CT-KUB are really low nowadays. The study by Lindqvist et al. did not show any real benefits regarding sick leave, medication or suffering with CT-KUB in the acute session [176]. But it was almost 20 years ago and the study has weaknesses as mentioned before. There is a need for a well performed randomized controlled trial (RCT), addressing whether to perform a radiological (CT-KUB) evaluation as promptly as possible, or whether we should continue with delayed evaluation of the stone disease. I hope that we as urologists find a way to make this RCT happen, preferably as soon as possible.

Future treatment perspectives

The workup of stone patients will be better in the future, with more information both on the stone and the patient. With objective measurements and facts, using computerized/AI programs, it will be possible to individualize procedures and deliver optimal stone treatment to every single patient [184].

ESWL will remain as the most important modality and be the "base" of stone surgery in the near future, as it is an outpatient and very cost-efficient technique.

The SFR we show of 72% is comparable to other studies and acceptable, but it can be improved.

The development of more efficient machines is slowly ongoing. Twin-head or tandem-pulse shock-wave generators will be available with automated location/tracking systems activated during treatment to make every shockwave hit the stone [185]. With these new tools ESWL has the potential to improve its results even more. Lowering the frequency to 1 Hz, adding abdominal compression, power-ramping and maybe standardized MET might further improve SFR results to some extent. Initiating ESWL at an earlier point might also improve results and reduce suffering for these patients [179]. It is feasible to perform multiple sessions of ESWL waiting only one day. This works safely for ureteral stones, shortening treatment time for these patients [186]. The latest and promising technical development is burst wave lithotripsy. It uses sinusoidal short bursts of focused ultrasonic pulses (200 Hz and 4 Mp) to fragment stones [3].

There is a need for better collection and storage of data on stone disease and outcomes. A national registry for stone patients would be most desirable. Built-in software enabling us to use the objective data measurements on the patient and stone, calculating risk of complications and predicting SFR outcome should be available in the "new" ESWL machines [185]. The foundations for creating a national stone register are now ongoing with the work of a Swedish national guideline on stone treatment. There is a genuine interest in starting up a national stone register; both Goteborg and Örebro University have presented plans for this and hopefully it will happen in the near future.

The technical development of URS (ureteroscopy) will continue, and better instruments, better flexibility/vision/irrigation and better lasers will take us a bit further. Laser development will continue; the latest more effective laser is the one with the Thulium laser fiber [138].

Problems constantly facing us when performing URS are the cost of the flexible instruments and their limited sustainability. Other problems are the contamination of these reusable instruments and increasing bacterial resistance. We are already using throwaway instruments today and whatever the environmental aspects of this might be, they are here to stay. Surprisingly, and to my fascination, these instruments work really well. A prediction would be that the use of throwaway instruments will increase. Their usage will initially be directed towards procedures with risk of damaging or contaminating the instruments. The reusable instruments will still remain in practice primarily for daily work, mostly cystoscopies. Reusable instruments will also remain in cancer treatment, where there is need for polarized light (NBI - narrow band imaging/Hexvix®), because these features are too expensive to incorporate in a throwaway instrument. Antegrade URS will be used more in the future. There are different techniques for antegrade URS: many use one-step dilators through a nephrostomy channel (applied around a week before the

surgery), then use the flexible ureteroscope when treating the stone. It is clear that the antegrade approach is safe, effective and that it offers a different and sometimes better approach to removing the stone. It may be possible that URS could reduce the stricture risk when treating proximal/complex or impacted stones [187].

PCNL is technically the most complex surgical procedure. It will be performed at fewer places in the future, probably "stone centres". Preferably these "stone centres" will have all modalities of stone treatment accessible. PCNL also demands a ward, able to handle postoperative care with knowledge of the procedure and its complications. The trend in PCNL has been to reduce the incision/access channel, making this an outpatient procedure or at least surgery with a very limited admission time. The mini PCNL works well especially for smaller lower calyceal stones. But PCNL is a treatment for a highly selected, small group of stone patients. The mini PCNL will have limited effects both on patient suffering and on treatment costs.

In the future it is likely that more stones can and will be managed by URS. This is driven by the fact that many urological clinics in Europe are privately owned. An ESWL machine and the need to admit patients for an over-night stay (PCNL) are probably regarded by private practitioners as an unnecessary burden, leaving them with URS as the only surgical "in house" option. This is acceptable if it is driven by the interests of the patient or for the improvement of urological procedures and not for profit. The length of and the need for hospital stay after stone surgery will decrease even more in the future. This is due to technical improvements in stone disintegration resulting in shorter operation time and less trauma to the patients.

The development of urological robotic surgery is now well established and has spread from robotically-assisted prostatectomies, to bladder and kidney operations, and further in the urological surgical field. The risk of stricture and the technical complexity of proximal and impacted stones emphasize the need for another approach. Robotic stone surgery could be that solution and it just might be able to improve the treatment results for these stones [188]. Robotic surgery could also work as an alternative to PCNL. Larger or multiple stones in the renal pelvis, especially if there are associated conditions like a PUJ-stenosis, could mean robotics are the best option.

For staghorn stones PCNL will remain the "gold standard", and most surgeons who have tried open stone surgery on staghorn stones would agree. The development of new materials of stents opens the possibility for long-term or even permanent use (like cardiac stents) in the future [189].

Conclusions

Paper I: Complications in Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study, conclusion: We conclude that there are few complications to modern ESWL treatment. 1 Hz should be used to reduce complications (p=0.025). As there is no indication that 1Hz is less effective than 1.5 Hz, this strongly implies that 1 Hz should normally be the frequency used.

Success rate with ESWL alone was high 71.8% (n=1324). Our data indicate that diabetes and larger stone size increase the risk of complications. The need for antiemetics during ESWL is a factor that deserves special consideration and further study. Distal stones seem to have a lower risk of complications (p=0.017).

Paper II: A study of clinical complications and possible risk factors for stone surgery - a population based study, conclusions: URS in a modern setting provides excellent results with high SFR and low morbidity. Preoperative stone size <4mm showed 100 % SFR success rate (n=112). SFR for stones >4≤6 mm was 96.2 % (n=176), for stones >6≤10 mm 84.6 % (n=193), and for stones >10 mm was 68.2 % (n=30). Time of day, or the presence of a urological specialized operating nurse does not affect the risk of complications and we found no other significant risk factors for complications. Regarding bacteria, *E. coli* is the most common in preoperative cultures. In this study the risk of complications increases with age. We conclude that for patients >65 years this should be considered in preoperative counselling.

Paper III: Percutaneous nephrolithotomy and modern aspects of complications and antibiotic treatment conclusions: Stone free rate was 65.6% (n=122) which is acceptable and comparable with other studies. This study has a total complication rate of 16%, with approximately 10% being severe. The most common complication of PCNL was infection at 60% (bleeding 5.4%, reoperation 1.6% and pain 0.5%). Our results regarding levels of *E. faecalis* in cultures, should be validated in a larger cohort, possibly with a higher rate of antibiotic resistance, before a change of guidelines regarding prophylactic antibiotics could be proposed. We conclude that the high prevalence of *E. faecalis* needs to be considered.

Paper IV: Factors influencing stone free rate of Extracorporeal Shock Wave Lithotripsy (ESWL): A cohort study conclusions: We conclude that stone maximum size/stone volume and age have an impact on stone free rate after ESWL. We are puzzled by age being such a strong predictor for SFR, and this needs to be further investigated.

Populärvetenskaplig sammanfattning

Sten i urinvägarna har drabbat människor i flera tusen år och finns beskrivet redan i gamla Egypten. Vi tror att stenbildning i äldre tider var vanligast i urinblåsan sekundärt till obehandlade infektioner och ofullständig blåstömning. I modern tid och i utvecklade länder är stenar i de övre urinvägarna det största problemet. Tillgången till mat och då inte minst kött, har förbättrat livsbetingelserna och har i kombination med andra vällevnadseffekter bidragit till en ökande sten-problematik. Vi vet också att ärftliga faktorer kan fördubbla risken för sten. Orsaken till att mineraler ansamlas i urinen och kristalliseras till stenar är multifaktoriell. Man kan beskriva detta detaljerat och komplicerat, men enkelt förklarat beror det på utsöndringen av mineraler (framför allt kalk, oxalat och fosfat), volymen vätska och pH i urinen. Dessa faktorer är styrande för när kristallisering/stenbildning uppstår, men de är alla påverkbara. Själva storleken på stenen har betydelse, små stenar (< 5 mm) trillar själv ut i ca 70% av fallen medan stenar större än 7 mm oftast kräver kirurgisk åtgärd. Sten i urinvägarna är ett växande problem. En ökning av antalet besök relaterade till njursten med mer än 50% har setts de sista 11 åren i Sverige.

När man börjar som ung kirurg är man främst fokuserad på kirurgisk teknik. Att kirurgi också är förenat med komplikationer och att sådana risker har en mycket stor betydelse för hur man skall råda och konsultera patienterna måste man också snabbt lära sig.

Denna avhandling fokuserar på komplikationer och behandlingsresultat vid behandling av urologisk stensjukdom. De klassiska komplikationerna till kirurgi är infektioner, blödningar och blodproppar. Inom stenkirurgi är stopp i urinvägarna, infektion och blödning de vanligaste riskerna eller komplikationerna. Mina studier har sin grund i mitt mångåriga arbete som urolog och den vilja jag hyser att förbättra vården för patienter med stensjukdom. Njurstenssjukdom är knappast något hot topic eller ett ”prestigeområde” inom den urologiska specialiteten men sjukdomen är och kommer att förbli mycket vanlig förekommande, så förekommande att den skulle kunna kallas en folksjukdom. Det vanligaste och bästa sättet att bli av med njursten om man drabbats av detta (jag har själv drabbats och upplevelsen är smärtsam) är att kroppen själv på egen hand stöter ut stenen tillsammans med urinen. Detta fungerar upp till ca 5 mm storlek på stenen med individuella variationer. Är stenen större fastnar den tyvärr gärna och gör då ofta ont. Stenen kan även orsaka att urinflödet stoppas och att njuren svullnar upp, så kallad vattennjure. Kortsiktigt har detta begränsad betydelse förutom att det också gör ordentligt ont, men på längre

sikt skadas njurens funktion och det finns ökad risk för infektioner som då kan bli livshotande.

Det gamla sättet att ta bort större eller fastsittande njur-/uretärstenar var öppen kirurgi. Lite ironisk beskrevs det ofta som det ”stora snittet för den lilla stenen”.

Det utvecklades på 1970- och 1980-talet bättre metoder att behandla njursten. En metod där man med ultraljud kan krossa stenen inne i kroppen benämnd ESWL (Extracorporal/utanför kroppen ShockWave/stötvåg Lithotripsi/slå sönder stenen) blev tillgänglig. Fortsatta tekniska framsteg gjorde det möjligt att utveckla så tunna kikare (kallade uretäroskop) att man kunde föra in dem via urinröret till urinblåsan och upp i urinledaren, ibland hela vägen upp till njurbäckenet. När man påträffade stenen kunde man skjuta sönder den med laser och vid behov dra ut större flisor (kallat URS=URetäroSkopi i min avhandling). De riktigt stora stenarna kan bara växa där det finns plats uppe i njurbäckenet, en annan teknik utvecklades där man finurligt och utan att egentligen skada njuren kunde punktera njurbäckenet. Genom att gradvis vidga hålet blir det möjligt att föra in en kikare, sönderdela och ta ut stenen (PCNL=PerCutan/genom huden Nefro/njuren Lithotomy/ta bort stenen).

Studierna i avhandlingen utgår från patienter här i Nordvästskåne. Det är både en styrka och svaghet att sten-studierna är gjorda lokalt. Det kan noteras att mina studier inkluderar alla opererade njurstenar med samtliga operationsmodaliteterna ESWL, URS och PCNL i nordvästra Skåne under drygt 5 år (studie I-III). Att representationen är lokalt begränsad och inte innefattar andra delar av Sverige och Europa kan förstås utgöra en svaghet. Studierna speglar den moderna kirurgin och beskriver alla metodernas förtjänster men också deras risker/komplikationer. Utöver detta har jag försökt hitta objektiva faktorer som påverkar resultatet, exempelvis sådant som man kan se på röntgen och ta hänsyn till när man planerar behandlingarna.

Slutsatserna i studie I är att ESWL fungerar bra (72% blir av med sin sten) med ganska liten risk för komplikationer (ca 6%). Ett ännu bättre resultat kan uppnås om man vid ESWL skjuter lite långsammare (1 Hz), vilket minskar risken för komplikationer samtidigt som resultatet förblir bra. Diabetes och större stenar ökar komplikationsrisken. Vi märkte att om patienten mådde illa (behövde medicin för detta) visade sig risken för komplikation också öka. Vår studie visade även, vilket var förväntat, att patienter med stenar långt nere i urinledaren hade mindre risk för komplikationer.

Slutsatserna i studie II: Risken för komplikationer vid URS var totalt högre än vid ESWL, drygt 10% men URS botar stenar bra (91% blir av med stenen). URS är ganska tekniskt krävande och ”pilligt”, vi trodde att med van personal och om operationen gjordes på dagen skulle resultatet påverkas till det bättre. Det kunde vi dock inte se i studien, vilket i och för sig är bra ur många perspektiv. Vi såg att risken för komplikationer ökade med åldern (URS är en operation med sövning etc

som kan vara riskfyllt för äldre). Kanske skall man vara lite försiktigare med URS för patienter över 65 års ålder.

Slutsatserna i studie III, PCNL-studien: Här är störst risk för komplikationer, totalt ca 16%. PCNL är den största och mest tidskrävande av alla ingreppen men den behövs hos ganska få patienter. 10% av komplikationerna var allvarliga och den vanligaste orsaken var infektion. PCNL behandlar svåra och stora stenar och man botar 66% med denna operation. Vi tittade på hur det såg ut med bakterier i stenen och urinen. Det är vanlig förekommande, ca 1/3 har bakterier. Det som var förvånande här var att *E.faecalis* var lika vanlig som den normalt vanligaste bakterien *E.coli*. Detta kan spela en viss roll. Det är nämligen så att våra vanligaste förebyggande antibiotikabehandlingar (profylax) biter dåligt på E. faecalis. Vår studie är för liten och möjligen för regionalt begränsad för att dra bestämda slutsatser av dessa resultat. Om resultaten kan reproduceras i övriga Sverige eller Europa finns kanske anledning att överväga ett byte till en annan antibiotikaprofylax som är effektiv mot båda dessa bakterier.

Studie IV: Faktorer som påverkar hur bra vi lyckas med ESWL (ännu inte publicerad) visar att stenens största mått och patientens ålder har betydelse för hur effektivt vi kan slå sönder stenen med ESWL. Dessa två objektiva parametrar skall därför beaktas innan man behandlar patienter med ESWL. Ju yngre man är och ju mindre stenen är ju större sannolikhet att behandlingsresultatet blir bra. Att åldern spelar en så stor roll förvånar oss och detta behöver man studera vidare. Vi hoppas också att våra data tillsammans med andra forskares resultat skall kunna ge oss en algoritm för att beräkna risken för komplikationer och sannolikheten för bot med ESWL.

Acknowledgments

I would like to thank:

The staff at the department of Urology, Helsingborg and Ängelholms hospital.

The Gorthon foundation, Lions foundation, Percy Falk foundation and ALF Region Skåne for their support.

The statistical Department at the University of Lund for aiding me in the statistical workup with the articles.

The medical hospital library in Helsingborg and their fantastic staff.

I am ever so grateful for open internet accessible archives and articles.

References

1. Lyu J, Wu R. [A brief history of recognition on urolithiasis before medieval period]. Zhonghua Yi Shi Za Zhi. 2014;44(1):36-9. Epub 2014/04/30. PubMed PMID: 24774894.
2. Lopez M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol. 2010;25(1):49-59. doi: 10.1007/s00467-008-0960-5. PubMed PMID: 21476230; PubMed Central PMCID: PMCPMC2778769.
3. Wein AJ. Campbell-Walsh-Wein Urology, Twelfth Edition. 12th ed. Alan W. Partin MD P, Roger R. Dmochowski MD, MMHC, FACS, Louis R. Kavoussi MD, MBA and Craig A. Peters MD, editor. Elsevier. 1600 John F. Kennedy Blvd.Ste 1600. Philadelphia,: Elsevier; 2020.
4. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2-3):e86-96. PubMed PMID: 20811557; PubMed Central PMCID: PMCPMC2931286.
5. Hesse A, Brandle E, Wilbert D, et al. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. European urology. 2003;44(6):709-13. PubMed PMID: 14644124.
6. Trinchieri A. Epidemiology of urolithiasis: an update. Clin Cases Miner Bone Metab. 2008;5(2):101-6. PubMed PMID: 22460989; PubMed Central PMCID: PMCPMC2781200.
7. Ljunghall S. Incidence and natural history of renal stone disease and its relationship to calcium metabolism. European urology. 1978;4(6):424-30. PubMed PMID: 216552.
8. Socialstyrelsen. Socialstyrelsen registerservise, statistik och data. In: omsorg SäSkfvo, editor. Web: Socialstyrelsen 2021.
9. Scales CD, Jr., Curtis LH, Norris RD, et al. Changing gender prevalence of stone disease. J Urol. 2007;177(3):979-82. Epub 2007/02/14. doi: 10.1016/j.juro.2006.10.069. PubMed PMID: 17296391.
10. Ahlstrand C, Tiselius HG. Recurrences during a 10-year follow-up after first renal stone episode. Urol Res. 1990;18(6):397-9. Epub 1990/01/01. PubMed PMID: 2100415.
11. Asplin JR, Mandel NS, Coe FL. Evidence of calcium phosphate supersaturation in the loop of Henle. Am J Physiol. 1996;270(4 Pt 2):F604-13. Epub 1996/04/01. doi: 10.1152/ajprenal.1996.270.4.F604. PubMed PMID: 8967338.
12. Kok DJ, Khan SR. Calcium oxalate nephrolithiasis, a free or fixed particle disease. Kidney Int. 1994;46(3):847-54. Epub 1994/09/01. doi: 10.1038/ki.1994.341. PubMed PMID: 7996806.

13. Ryall RL, Harnett RM, Marshall VR. The effect of urine, pyrophosphate, citrate, magnesium and glycosaminoglycans on the growth and aggregation of calcium oxalate crystals in vitro. Clin Chim Acta. 1981;112(3):349-56. Epub 1981/05/01. doi: 10.1016/0009-8981(81)90458-7. PubMed PMID: 6263523.
14. Worcester EM, Beshensky AM. Osteopontin inhibits nucleation of calcium oxalate crystals. Ann N Y Acad Sci. 1995;760:375-7. Epub 1995/04/21. doi: 10.1111/j.1749-6632.1995.tb44661.x. PubMed PMID: 7785921.
15. Evan AP, Coe FL, Lingeman JE, et al. Mechanism of formation of human calcium oxalate renal stones on Randall's plaque. Anat Rec (Hoboken). 2007;290(10):1315-23. Epub 2007/08/29. doi: 10.1002/ar.20580. PubMed PMID: 17724713.
16. Dorian HH, Rez P, Drach GW. Evidence for aggregation in oxalate stone formation: atomic force and low voltage scanning electron microscopy. J Urol. 1996;156(5):1833-7. Epub 1996/11/01. doi: 10.1016/s0022-5347(01)65547-2. PubMed PMID: 8863626.
17. Grases F, Costa-Bauza A, Conte A. Studies on structure of calcium oxalate monohydrate renal papillary calculi. Mechanism of formation. Scanning Microsc. 1993;7(3):1067-73; discussion 73-4. Epub 1993/09/01. PubMed PMID: 8146607.
18. Khan SR. Calcium oxalate crystal interaction with renal tubular epithelium, mechanism of crystal adhesion and its impact on stone development. Urol Res. 1995;23(2):71-9. Epub 1995/01/01. doi: 10.1007/BF00307936. PubMed PMID: 7676537.
19. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med. 1992;327(16):1141-52. Epub 1992/10/15. doi: 10.1056/NEJM199210153271607. PubMed PMID: 1528210.
20. C. Türk (Chair) AN, A. Petřík, C. Seitz, A. Skolarikos (Vice-chair), B. Somani, K. Thomas, G. Gambaro (Consultant nephrologist), Guidelines Associates: N.F. Davis JFD, R. Lombardo, L. Tzelves. EAU Guidelines on Urolithiasis 2021. Available from: https://uroweb.org/guideline/urolithiasis/.
21. Khan SR, Hackett RL. Role of organic matrix in urinary stone formation: an ultrastructural study of crystal matrix interface of calcium oxalate monohydrate stones. J Urol. 1993;150(1):239-45. Epub 1993/07/01. doi: 10.1016/s0022-5347(17)35454-x. PubMed PMID: 8510264.
22. Cloutier J, Villa L, Traxer O, et al. Kidney stone analysis: "Give me your stone, I will tell you who you are!". World J Urol. 2015;33(2):157-69. Epub 2014/12/04. doi: 10.1007/s00345-014-1444-9. PubMed PMID: 25465911; PubMed Central PMCID: PMCPMC4308647.
23. Hedelin H. Uropathogens and urinary tract concretion formation and catheter encrustations. Int J Antimicrob Agents. 2002;19(6):484-7. Epub 2002/07/24. doi: 10.1016/s0924-8579(02)00095-x. PubMed PMID: 12135838.
24. Segura JW, Preminger GM, Assimos DG, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol. 1997;158(5):1915-21. Epub 1997/10/23 22:31. PubMed PMID: 9334635.

25. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. J Nephrol. 2000;13 Suppl 3:S45-50. PubMed PMID: 11132032.
26. Moe OW, Abate N, Sakhaee K. Pathophysiology of uric acid nephrolithiasis. Endocrinol Metab Clin North Am. 2002;31(4):895-914. Epub 2002/12/12. doi: 10.1016/s0889-8529(02)00032-4. PubMed PMID: 12474637.
27. Sorokin I, Mamoulakis C, Miyazawa K, et al. Epidemiology of stone disease across the world. World J Urol. 2017;35(9):1301-20. Epub 2017/02/19. doi: 10.1007/s00345-017-2008-6. PubMed PMID: 28213860.
28. Taylor EN, Stampfer MJ, Curhan GC. Fatty acid intake and incident nephrolithiasis. Am J Kidney Dis. 2005;45(2):267-74. Epub 2005/02/03. doi: 10.1053/j.ajkd.2004.09.026. PubMed PMID: 15685503.
29. Ahmed MH, Ahmed HT, Khalil AA. Renal stone disease and obesity: what is important for urologists and nephrologists? Ren Fail. 2012;34(10):1348-54. Epub 2012/09/28. doi: 10.3109/0886022X.2012.723777. PubMed PMID: 23013150.
30. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293(4):455-62. Epub 2005/01/27. doi: 10.1001/jama.293.4.455. PubMed PMID: 15671430.
31. Turk C, Petrik A, Sarica K, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. European urology. 2016;69(3):468-74. doi: 10.1016/j.eururo.2015.07.040. PubMed PMID: 26318710.
32. Abdel-Halim RE, Abdel-Halim MR. A review of urinary stone analysis techniques. Saudi Med J. 2006;27(10):1462-7. Epub 2006/10/03. PubMed PMID: 17013464.
33. Solak V, Gokce MI, Yaman O. Potassium citrate vs. hydrochlorothiazide to reduce urinary calcium excretion in calcium oxalate stone patients with hypercalciuria: a prospective randomized study. International urology and nephrology. 2021. Epub 2021/04/28. doi: 10.1007/s11255-021-02879-7. PubMed PMID: 33904027.
34. Zerwekh JE, Hughes MR, Reed BY, et al. Evidence for normal vitamin D receptor messenger ribonucleic acid and genotype in absorptive hypercalciuria. J Clin Endocrinol Metab. 1995;80(10):2960-5. Epub 1995/10/01. doi: 10.1210/jcem.80.10.7559881. PubMed PMID: 7559881.
35. Levi M, Breusegem S. Renal phosphate-transporter regulatory proteins and nephrolithiasis. N Engl J Med. 2008;359(11):1171-3. Epub 2008/09/12. doi: 10.1056/NEJMe0805943. PubMed PMID: 18784108; PubMed Central PMCID: PMCPMC2738939.
36. Ha YS, Tchey DU, Kang HW, et al. Phosphaturia as a promising predictor of recurrent stone formation in patients with urolithiasis. Korean journal of urology. 2010;51(1):54-9. Epub 2010/04/24. doi: 10.4111/kju.2010.51.1.54. PubMed PMID: 20414412; PubMed Central PMCID: PMCPMC2855459.
37. Holmes RP, Assimos DG. The impact of dietary oxalate on kidney stone formation. Urol Res. 2004;32(5):311-6. Epub 2004/06/29. doi: 10.1007/s00240-004-0437-3. PubMed PMID: 15221245.
38. Sinha MK, Collazo-Clavell ML, Rule A, et al. Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery. Kidney Int. 2007;72(1):100-7. Epub 2007/03/23. doi: 10.1038/sj.ki.5002194. PubMed PMID: 17377509.

39. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol. 2008;3(5):1453-60. Epub 2008/07/25. doi: 10.2215/CJN.01410308. PubMed PMID: 18650406; PubMed Central PMCID: PMCPMC2518810.

40. Asplin JR. Uric acid stones. Semin Nephrol. 1996;16(5):412-24. Epub 1996/09/01. PubMed PMID: 8890397.

41. Coe FL. Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria, or no metabolic disorder. Ann Intern Med. 1977;87(4):404-10. Epub 1977/10/01. doi: 10.7326/0003-4819-87-4-404. PubMed PMID: 907239.

42. Coe FL, Raisen L. Allopurinol treatment of uric-acid disorders in calcium-stone formers. Lancet. 1973;1(7795):129-31. Epub 1973/01/20. doi: 10.1016/s0140-6736(73)90197-9. PubMed PMID: 4118468.

43. Abu-Alfa AK, Younes A. Tumor lysis syndrome and acute kidney injury: evaluation, prevention, and management. Am J Kidney Dis. 2010;55(5 Suppl 3):S1-13; quiz S4-9. Epub 2010/04/28. doi: 10.1053/j.ajkd.2009.10.056. PubMed PMID: 20420966.

44. Das P, Gupta G, Velu V, et al. Formation of struvite urinary stones and approaches towards the inhibition-A review. Biomed Pharmacother. 2017;96:361-70. Epub 2017/10/14. doi: 10.1016/j.biopha.2017.10.015. PubMed PMID: 29028588.

45. Melessen IM, Henderickx MM, Merkx MM, et al. The effect of additional drug therapy as metaphylaxis in patients with cystinuria: a systematic review. Minerva Urol Nefrol. 2020;72(4):427-40. Epub 2020/02/23. doi: 10.23736/S0393-2249.20.03704-2. PubMed PMID: 32083421.

46. Wu DS, Stoller ML. Indinavir urolithiasis. Curr Opin Urol. 2000;10(6):557-61. Epub 2001/01/10. doi: 10.1097/00042307-200011000-00004. PubMed PMID: 11148725.

47. Howles SA, Thakker RV. Genetics of kidney stone disease. Nat Rev Urol. 2020;17(7):407-21. Epub 2020/06/14. doi: 10.1038/s41585-020-0332-x. PubMed PMID: 32533118.

48. Maddahi N, Aghamir SMK, Moddaresi SS, et al. The association of Dietary Approaches to Stop Hypertension-style diet with urinary risk factors of kidney stones formation in men with nephrolithiasis. Clin Nutr ESPEN. 2020;39:173-9. Epub 2020/08/30. doi: 10.1016/j.clnesp.2020.06.021. PubMed PMID: 32859313.

49. Ferraro PM, Curhan GC, Gambaro G, et al. Total, Dietary, and Supplemental Vitamin C Intake and Risk of Incident Kidney Stones. Am J Kidney Dis. 2016;67(3):400-7. doi: 10.1053/j.ajkd.2015.09.005. PubMed PMID: 26463139; PubMed Central PMCID: PMCPMC4769668.

50. Borghi L, Meschi T, Amato F, et al. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol. 1996;155(3):839-43. Epub 1996/03/01. PubMed PMID: 8583588.

51. Harvey JA, Hill KD, Pak CY. Similarity of urinary risk factors among stone-forming patients in five regions of the United States. J Lithotr Stone Dis. 1990;2(2):124-32. Epub 1990/04/01. PubMed PMID: 11536931.

52. Worcester EM. Stones from bowel disease. Endocrinol Metab Clin North Am. 2002;31(4):979-99. Epub 2002/12/12. doi: 10.1016/s0889-8529(02)00035-x. PubMed PMID: 12474641.

53. Lemann J, Jr., Pleuss JA, Worcester EM, et al. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. Kidney Int. 1996;49(1):200-8. Epub 1996/01/01. doi: 10.1038/ki.1996.27. PubMed PMID: 8770968.

54. Dent CE, Senior B. Studies on the treatment of cystinuria. Br J Urol. 1955;27(4):317-32. Epub 1955/12/01. doi: 10.1111/j.1464-410x.1955.tb03486.x. PubMed PMID: 13276628.

55. Garfield K, Leslie SW. Medullary Sponge Kidney. StatPearls. Treasure Island (FL)2020.

56. Islam AK, Holt S, Reisch J, et al. What Predicts Recurrent Kidney Stone after Parathyroidectomy in Patients with Primary Hyperparathyroidism? J Am Coll Surg. 2020;231(1):74-82. Epub 2020/04/25. doi: 10.1016/j.jamcollsurg.2020.04.015. PubMed PMID: 32330575.

57. Usui Y, Matsuzaki S, Matsushita K, et al. Urinary citrate in kidney stone disease. Tokai J Exp Clin Med. 2003;28(2):65-70. Epub 2004/01/13. PubMed PMID: 14714831.

58. Domrongkitchaiporn S, Stitchantrakul W, Kochakarn W. Causes of hypocitraturia in recurrent calcium stone formers: focusing on urinary potassium excretion. Am J Kidney Dis. 2006;48(4):546-54. Epub 2006/09/26. doi: 10.1053/j.ajkd.2006.06.008. PubMed PMID: 16997050.

59. Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med. 1995;98(1):50-9. Epub 1995/01/01. doi: 10.1016/S0002-9343(99)80080-1. PubMed PMID: 7825619.

60. Barry KA. Citrate Salts for Preventing and Treating Calcium-Containing Kidney Stones in Adults. Am Fam Physician. 2017;95(9):552-3. Epub 2017/07/04. PubMed PMID: 28671385.

61. Phillips R, Hanchanale VS, Myatt A, et al. Citrate salts for preventing and treating calcium containing kidney stones in adults. Cochrane Database Syst Rev. 2015(10):CD010057. Epub 2015/10/07. doi: 10.1002/14651858.CD010057.pub2. PubMed PMID: 26439475.

62. Kok DJ, Papapoulos SE, Blomen LJ, et al. Modulation of calcium oxalate monohydrate crystallization kinetics in vitro. Kidney Int. 1988;34(3):346-50. Epub 1988/09/01. doi: 10.1038/ki.1988.187. PubMed PMID: 2459439.

63. Lieske JC, Leonard R, Toback FG. Adhesion of calcium oxalate monohydrate crystals to renal epithelial cells is inhibited by specific anions. Am J Physiol. 1995;268(4 Pt 2):F604-12. Epub 1995/04/01. doi: 10.1152/ajprenal.1995.268.4.F604. PubMed PMID: 7733317.

64. Tzelves L, Mourmouris P, Skolarikos A. Comparison of current guidelines on medical management of stone disease. Archivos espanoles de urologia. 2021;74(1):171-82. Epub 2021/01/19. PubMed PMID: 33459633.

65. Massey L. Magnesium therapy for nephrolithiasis. Magnes Res. 2005;18(2):123-6. Epub 2005/08/17. PubMed PMID: 16100850.

66. Fleisch H. Inhibitors and promoters of stone formation. Kidney Int. 1978;13(5):361-71. Epub 1978/05/01. doi: 10.1038/ki.1978.54. PubMed PMID: 351264.

67. Grases F, Conte A. Urolithiasis, inhibitors and promoters. Urol Res. 1992;20(1):86-8. Epub 1992/01/01. doi: 10.1007/BF00294344. PubMed PMID: 1736493.

68. Marshall VR, Ryall RL. Investigation of urinary calculi. Br J Hosp Med. 1981;26(4):389-92. Epub 1981/10/01. PubMed PMID: 7306741.

69. Kanashiro A, Angerri O. [Urinary pH relevance on urolithiasis management.]. Archivos espanoles de urologia. 2021;74(1):102-11. Epub 2021/01/19. PubMed PMID: 33459626.

70. Nguyen QV, Kalin A, Drouve U, et al. Sensitivity to meat protein intake and hyperoxaluria in idiopathic calcium stone formers. Kidney Int. 2001;59(6):2273-81. Epub 2001/05/31. doi: 10.1046/j.1523-1755.2001.00744.x. PubMed PMID: 11380831.

71. Curhan GC, Willett WC, Speizer FE, et al. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol. 1999;10(4):840-5. Epub 1999/04/15. doi: 10.1681/ASN.V104840. PubMed PMID: 10203369.

72. Eisner BH, Goldfarb DS, Baum MA, et al. Evaluation and Medical Management of Patients with Cystine Nephrolithiasis: A Consensus Statement. J Endourol. 2020;34(11):1103-10. Epub 2020/02/19. doi: 10.1089/end.2019.0703. PubMed PMID: 32066273.

73. Ferraro PM, Taylor EN, Gambaro G, et al. Caffeine intake and the risk of kidney stones. Am J Clin Nutr. 2014;100(6):1596-603. doi: 10.3945/ajcn.114.089987. PubMed PMID: 25411295; PubMed Central PMCID: PMCPMC4232021.

74. Barghouthy Y, Corrales M, Doizi S, et al. Tea and coffee consumption and pathophysiology related to kidney stone formation: a systematic review. World J Urol. 2020. Epub 2020/10/15. doi: 10.1007/s00345-020-03466-8. PubMed PMID: 33052484.

75. Micali S, Sighinolfi MC, Celia A, et al. Can Phyllanthus niruri affect the efficacy of extracorporeal shock wave lithotripsy for renal stones? A randomized, prospective, long-term study. J Urol. 2006;176(3):1020-2. Epub 2006/08/08. doi: 10.1016/j.juro.2006.04.010. PubMed PMID: 16890682.

76. van Rooijen JJ, Voskamp AF, Kamerling JP, et al. Glycosylation sites and site-specific glycosylation in human Tamm-Horsfall glycoprotein. Glycobiology. 1999;9(1):21-30. Epub 1999/01/13. doi: 10.1093/glycob/9.1.21. PubMed PMID: 9884403.

77. Aggarwal KP, Narula S, Kakkar M, et al. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. Biomed Res Int. 2013;2013:292953. Epub 2013/10/24. doi: 10.1155/2013/292953. PubMed PMID: 24151593; PubMed Central PMCID: PMCPMC3787572.

78. Jones P, Karim Sulaiman S, Gamage KN, et al. Do Lifestyle Factors Including Smoking, Alcohol, and Exercise Impact Your Risk of Developing Kidney Stone

Disease? Outcomes of a Systematic Review. J Endourol. 2021;35(1):1-7. Epub 2020/08/19. doi: 10.1089/end.2020.0378. PubMed PMID: 32808537.

79. Ferraro PM, Curhan GC, Sorensen MD, et al. Physical activity, energy intake and the risk of incident kidney stones. J Urol. 2015;193(3):864-8. doi: 10.1016/j.juro.2014.09.010. PubMed PMID: 25229560; PubMed Central PMCID: PMCPMC4378568.
80. Sorensen MD, Chi T, Shara NM, et al. Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: a report from the Women's Health Initiative. J Am Soc Nephrol. 2014;25(2):362-9. Epub 2013/12/18. doi: 10.1681/ASN.2013050548. PubMed PMID: 24335976; PubMed Central PMCID: PMCPMC3904570.
81. Irving RA, Noakes TD, Rodgers AL, et al. Crystalluria in marathon runners. 1. Standard marathon--males. Urol Res. 1986;14(6):289-94. Epub 1986/01/01. doi: 10.1007/BF00262377. PubMed PMID: 3811077.
82. Liu B, Balkwill A, Roddam A, et al. Separate and joint effects of alcohol and smoking on the risks of cirrhosis and gallbladder disease in middle-aged women. Am J Epidemiol. 2009;169(2):153-60. Epub 2008/11/27. doi: 10.1093/aje/kwn280. PubMed PMID: 19033524.
83. Li W, Mao Y, Lu C, et al. Role of Sexual Intercourse after Shockwave Lithotripsy for Distal Ureteral Stones: A Randomized Controlled Trial. Urol J. 2020;17(2):134-8. Epub 2020/03/18. doi: 10.22037/uj.v0i0.5400. PubMed PMID: 32180212.
84. Pedro RN, Aslam AU, Bello JO, et al. Nutrients, vitamins, probiotics and herbal products: an update of their role in urolithogenesis. Urolithiasis. 2020;48(4):285-301. Epub 2020/03/04. doi: 10.1007/s00240-020-01182-x. PubMed PMID: 32123972.
85. Wong Y, Cook P, Roderick P, et al. Metabolic Syndrome and Kidney Stone Disease: A Systematic Review of Literature. J Endourol. 2016;30(3):246-53. Epub 2015/11/19. doi: 10.1089/end.2015.0567. PubMed PMID: 26576717.
86. Haghighatdoost F, Sadeghian R, Clark CCT, et al. Higher Dietary Acid Load Is Associated With an Increased Risk of Calcium Oxalate Kidney Stones. J Ren Nutr. 2020. Epub 2020/09/29. doi: 10.1053/j.jrn.2020.08.012. PubMed PMID: 32981831.
87. Ormanji MS, Rodrigues FG, Heilberg IP. Dietary Recommendations for Bariatric Patients to Prevent Kidney Stone Formation. Nutrients. 2020;12(5). Epub 2020/05/21. doi: 10.3390/nu12051442. PubMed PMID: 32429374; PubMed Central PMCID: PMCPMC7284744.
88. Jendeberg J, Geijer H, Alshamari M, et al. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. Eur Radiol. 2017;27(11):4775-85. Epub 2017/06/09. doi: 10.1007/s00330-017-4852-6. PubMed PMID: 28593428; PubMed Central PMCID: PMCPMC5635101.
89. Yallappa S, Amer T, Jones P, et al. Natural History of Conservatively Managed Ureteral Stones: Analysis of 6600 Patients. J Endourol. 2018;32(5):371-9. Epub 2018/02/28. doi: 10.1089/end.2017.0848. PubMed PMID: 29482379.
90. Damber J-E, Peeker R. Urologi. Damber J-E, Peeker R, editors. Lund: Studentliteratur; 2012. 1-549 p.
91. Uvelius B. Urologi historia-Några droppar från ett stort flöde. 1 ed2020.

92. Fernstrom I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10(3):257-9. Epub 1976/01/01. doi: 10.1080/21681805.1976.11882084. PubMed PMID: 1006190.

93. El-Wahab OA, El-Tabey MA, El-Barky E, et al. Multislice computed tomography vs. intravenous urography for planning supine percutaneous nephrolithotomy: A randomised clinical trial. Arab J Urol. 2014;12(2):162-7. Epub 2015/05/29. doi: 10.1016/j.aju.2013.11.005. PubMed PMID: 26019942; PubMed Central PMCID: PMCPMC4434608.

94. Xiang H, Chan M, Brown V, et al. Systematic review and meta-analysis of the diagnostic accuracy of low-dose computed tomography of the kidneys, ureters and bladder for urolithiasis. J Med Imaging Radiat Oncol. 2017;61(5):582-90. Epub 2017/02/01. doi: 10.1111/1754-9485.12587. PubMed PMID: 28139077.

95. Poletti PA, Platon A, Rutschmann OT, et al. Low-dose versus standard-dose CT protocol in patients with clinically suspected renal colic. AJR Am J Roentgenol. 2007;188(4):927-33. Epub 2007/03/23. doi: 10.2214/AJR.06.0793. PubMed PMID: 17377025.

96. Ray AA, Ghiculete D, Pace KT, et al. Limitations to ultrasound in the detection and measurement of urinary tract calculi. Urology. 2010;76(2):295-300. Epub 2010/03/09. doi: 10.1016/j.urology.2009.12.015. PubMed PMID: 20206970.

97. Niwa N, Matsumoto K, Miyahara M, et al. Simple and practical nomograms for predicting the stone-free rate after shock wave lithotripsy in patients with a solitary upper ureteral stone. World J Urol. 2017;35(9):1455-61. doi: 10.1007/s00345-017-2014-8. PubMed PMID: 28220189.

98. Bigum LH, Ulriksen PS, Omar OS. Using a three-dimensional computer assisted stone volume estimates to evaluate extracorporeal shockwave lithotripsy treatment of kidney stones. Urolithiasis. 2016;44(5):451-7. doi: 10.1007/s00240-016-0864-y. PubMed PMID: 26914829.

99. Mullhaupt G, Engeler DS, Schmid HP, et al. How do stone attenuation and skin-to-stone distance in computed tomography influence the performance of shock wave lithotripsy in ureteral stone disease? BMC urology. 2015;15:72. Epub 2015/07/24. doi: 10.1186/s12894-015-0069-7. PubMed PMID: 26201514; PubMed Central PMCID: PMCPMC4511972.

100. Choi JW, Song PH, Kim HT. Predictive factors of the outcome of extracorporeal shockwave lithotripsy for ureteral stones. Korean journal of urology. 2012;53(6):424-30. Epub 2012/06/29. doi: 10.4111/kju.2012.53.6.424. PubMed PMID: 22741053; PubMed Central PMCID: PMCPMC3382694.

101. Park BH, Choi H, Kim JB, et al. Analyzing the effect of distance from skin to stone by computed tomography scan on the extracorporeal shock wave lithotripsy stone-free rate of renal stones. Korean journal of urology. 2012;53(1):40-3. Epub 2012/02/11. doi: 10.4111/kju.2012.53.1.40. PubMed PMID: 22323973; PubMed Central PMCID: PMCPMC3272555.

102. Bandi G, Meiners RJ, Pickhardt PJ, et al. Stone measurement by volumetric three-dimensional computed tomography for predicting the outcome after extracorporeal shock wave lithotripsy. BJU Int. 2009;103(4):524-8. doi: 10.1111/j.1464-410X.2008.08069.x. PubMed PMID: 19007365.

103. Perks AE, Schuler TD, Lee J, et al. Stone attenuation and skin-to-stone distance on computed tomography predicts for stone fragmentation by shock wave lithotripsy. Urology. 2008;72(4):765-9. doi: 10.1016/j.urology.2008.05.046. PubMed PMID: 18674803.

104. Dahlman P, Dahlman PC, Akademiska sjukhuset U, et al. Rekommendationer för mätning av urinvägskonkrement/SURF:s kontrastmedelsgrupp, Version 1.0/2021-03-16. 2021.

105. Rompsaithong U, Jongjitaree K, Korpraphong P, et al. Characterization of renal stone composition by using fast kilovoltage switching dual-energy computed tomography compared to laboratory stone analysis: a pilot study. Abdom Radiol (NY). 2019;44(3):1027-32. Epub 2018/09/28. doi: 10.1007/s00261-018-1787-6. PubMed PMID: 30259102.

106. El-Nahas AR, El-Assmy AM, Mansour O, et al. A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock wave lithotripsy: the value of high-resolution noncontrast computed tomography. European urology. 2007;51(6):1688-93; discussion 93-4. Epub 2006/12/13. doi: 10.1016/j.eururo.2006.11.048. PubMed PMID: 17161522.

107. Hirsch B, Abt D, Gusewell S, et al. Outcome groups and a practical tool to predict success of shock wave lithotripsy in daily clinical routine. World J Urol. 2021;39(3):943-51. Epub 2020/05/22. doi: 10.1007/s00345-020-03253-5. PubMed PMID: 32436072.

108. Thiruchelvam N, Mostafid H, Ubhayakar G. Planning percutaneous nephrolithotomy using multidetector computed tomography urography, multiplanar reconstruction and three-dimensional reformatting. BJU Int. 2005;95(9):1280-4. Epub 2005/05/17. doi: 10.1111/j.1464-410X.2005.05519.x. PubMed PMID: 15892817.

109. Dunn PM, Keller RT, Jones SR. The absence of hematuria in patients with symptomatic urinary tract stones. West J Med. 1985;142(5):717-9. PubMed PMID: 4013291; PubMed Central PMCID: PMCPMC1306170.

110. Koenig CJ, Lindbloom EJ. Accuracy of hematuria in diagnosing kidney stones. J Fam Pract. 1999;48(11):912-3. PubMed PMID: 10907632.

111. Mefford JM, Tungate RM, Amini L, et al. A Comparison of Urolithiasis in the Presence and Absence of Microscopic Hematuria in the Emergency Department. West J Emerg Med. 2017;18(4):775-9. Epub 2017/06/15. doi: 10.5811/westjem.2017.4.33018. PubMed PMID: 28611901; PubMed Central PMCID: PMCPMC5468086 are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

112. Porena M, Guiggi P, Balestra A, et al. Pain killers and antibacterial therapy for kidney colic and stones. Urologia internationalis. 2004;72 Suppl 1:34-9. Epub 2004/05/11. doi: 10.1159/000076589. PubMed PMID: 15133331.

113. Garcia-Perdomo HA, Echeverria-Garcia F, Lopez H, et al. Pharmacologic interventions to treat renal colic pain in acute stone episodes: Systematic review and

meta-analysis. Prog Urol. 2017;27(12):654-65. Epub 2017/06/28. doi: 10.1016/j.purol.2017.05.011. PubMed PMID: 28651994.

114. Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ. 2016;355:i6112. doi: 10.1136/bmj.i6112. PubMed PMID: 27908918; PubMed Central PMCID: PMCPMC5131734 at http://www.icmje.org/coi_disclosure.pdf and declare: JMH received research grants from the Agency for Healthcare Research and Quality, the Urology Care Foundation, and Blue Cross Blue Shield of Michigan during the conduct of this study.
115. Kerr WS. Effects of Complete Ureteral Obstruction in Dogs on Kidney Function. American Journal of Physiology. 1956.
116. Ramsey S, Robertson A, Ablett MJ, et al. Evidence-based drainage of infected hydronephrosis secondary to ureteric calculi. J Endourol. 2010;24(2):185-9. Epub 2010/01/13. doi: 10.1089/end.2009.0361. PubMed PMID: 20063999.
117. Pearle MS, Pierce HL, Miller GL, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. J Urol. 1998;160(4):1260-4. Epub 1998/09/29. PubMed PMID: 9751331.
118. Ye Z, Zeng G, Yang H, et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. European urology. 2018;73(3):385-91. Epub 2017/11/16. doi: 10.1016/j.eururo.2017.10.033. PubMed PMID: 29137830.
119. Tiselius HG, Hellgren E, Andersson A, et al. Minimally invasive treatment of infection staghorn stones with shock wave lithotripsy and chemolysis. Scand J Urol Nephrol. 1999;33(5):286-90. Epub 1999/11/26. PubMed PMID: 10572989.
120. Lee YH, Chang LS, Chen MT, et al. Local chemolysis of obstructive uric acid stone with 0.1 M THAM and 0.02% chlorhexidine. Urologia internationalis. 1993;51(3):147-51. Epub 1993/01/01. doi: 10.1159/000282533. PubMed PMID: 8249225.
121. Kipling M, Mohammed A, Medding RN. Guidewires in clinical practice: applications and troubleshooting. Expert Rev Med Devices. 2009;6(2):187-95. Epub 2009/03/21. doi: 10.1586/17434440.6.2.187. PubMed PMID: 19298165.
122. Lunderquist A, Lunderquist M, Owman T. Guide wire for percutaneous transhepatic cholangiography. Radiology. 1979;132(1):228. Epub 1979/07/01. doi: 10.1148/132.1.228a. PubMed PMID: 451208.
123. Schönebeck J. Blåskatetern och dess bruk. 1 ed: Astra Tec AB; 1997. 1-59 p.
124. Carr HA. A short history of the Foley catheter: from handmade instrument to infection-prevention device. J Endourol. 2000;14(1):5-8. Epub 2000/03/29. doi: 10.1089/end.2000.14.5. PubMed PMID: 10735566.
125. Ellis H. Therapeutic milestones. The Foley catheter. Br J Clin Pract. 1988;42(6):248-9. Epub 1988/06/01. PubMed PMID: 3061431.
126. R.A M. History of urethral catheters and their balloons: drainage, anchorage, dilation, and hemostasis. J Endourology. 1993;7:89-92. doi: 10.1089/end.1993.7.89. PubMed Central PMCID: PMC8518833.

127. Camacho MF, Pereiras R, Carrion H, et al. Double-ended pigtail ureteral stent: useful modification to single end ureteral stent. Urology. 1979;13(5):516-20. Epub 1979/05/01. doi: 10.1016/0090-4295(79)90461-8. PubMed PMID: 442376.

128. Turk C, Petrik A, Sarica K, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. European urology. 2016;69(3):475-82. doi: 10.1016/j.eururo.2015.07.041. PubMed PMID: 26344917.

129. Marien T, Miller NL. Treatment of the Infected Stone. Urol Clin North Am. 2015;42(4):459-72. doi: 10.1016/j.ucl.2015.05.009. PubMed PMID: 26475943.

130. Marien T, Mass AY, Shah O. Antimicrobial resistance patterns in cases of obstructive pyelonephritis secondary to stones. Urology. 2015;85(1):64-8. Epub 2014/12/23. doi: 10.1016/j.urology.2014.10.007. PubMed PMID: 25530365.

131. Lynch MF, Anson KM, Patel U. Current opinion amongst radiologists and urologists in the UK on percutaneous nephrostomy and ureteric stent insertion for acute renal unobstruction: Results of a postal survey. BJU Int. 2006;98(6):1143-4. Epub 2006/11/28. doi: 10.1111/j.1464-410X.2006.06513.x. PubMed PMID: 17125470.

132. Wang CJ, Hsu CS, Chen HW, et al. Percutaneous nephrostomy versus ureteroscopic management of sepsis associated with ureteral stone impaction: a randomized controlled trial. Urolithiasis. 2016;44(5):415-9. Epub 2015/12/15. doi: 10.1007/s00240-015-0852-7. PubMed PMID: 26662171.

133. Sanford TH, Myers F, Chi T, et al. Emphysematous pyelonephritis: the impact of urolithiasis on disease severity. Transl Androl Urol. 2016;5(5):774-9. doi: 10.21037/tau.2016.07.02. PubMed PMID: 27785435; PubMed Central PMCID: PMCPMC5071188.

134. Skolarikos A, Alivizatos G, de la Rosette J. Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. European urology. 2006;50(5):981-90; discussion 90. Epub 2006/02/17. doi: 10.1016/j.eururo.2006.01.045. PubMed PMID: 16481097.

135. Tiselius HG, Chaussy CG. Arguments for choosing extracorporeal shockwave lithotripsy for removal of urinary tract stones. Urolithiasis. 2015;43(5):387-96. Epub 2015/09/01. doi: 10.1007/s00240-015-0818-9. PubMed PMID: 26315364.

136. Sabnis RB, Balaji SS, Sonawane PL, et al. EMS Lithoclast Trilogy: an effective single-probe dual-energy lithotripter for mini and standard PCNL. World J Urol. 2020;38(4):1043-50. Epub 2019/06/10. doi: 10.1007/s00345-019-02843-2. PubMed PMID: 31177306.

137. Aldoukhi AH, Hall TL, Ghani KR, et al. Response to Wollin re: "Strike Rate: Analysis of Laser Fiber to Stone Distance During Different Modes of Laser Lithotripsy". J Endourol. 2021;35(3):361. Epub 2021/02/18. doi: 10.1089/end.2021.29105.aha. PubMed PMID: 33595359.

138. Keller EX, De Coninck V, Doizi S, et al. Thulium fiber laser: ready to dust all urinary stone composition types? World J Urol. 2021;39(6):1693-8. Epub 2020/05/05. doi: 10.1007/s00345-020-03217-9. PubMed PMID: 32363450.

139. Chaussy C, Eisenberger F, Forssmann B. Extracorporeal shockwave lithotripsy (ESWL): a chronology. J Endourol. 2007;21(11):1249-53. Epub 2007/11/29. doi: 10.1089/end.2007.9880. PubMed PMID: 18042010.

140. Musa AA. Use of double-J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. International urology and nephrology. 2008;40(1):19-22. doi: 10.1007/s11255-006-9030-8. PubMed PMID: 17394095.
141. Chaussy C, Tailly GG, Forssmann B, et al. Exracorporeal Shock Wave Lithotripsy in a Nutshell. 2nd ed: Dornier MedTech Europe GmbH; 2015. 1-53 p.
142. Osthler PDPJ. The Stone Handbook. Italy: Edizioni Scripta Manent snc; 2013. 343 p.
143. Tiselius HG, Ackermann D, Alken P, et al. Guidelines on urolithiasis. European urology. 2001;40(4):362-71. PubMed PMID: 11713390.
144. Carlsson P, Kinn AC, Tiselius HG, et al. Cost effectiveness of extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy for medium-sized kidney stones. A randomised clinical trial. Scand J Urol Nephrol. 1992;26(3):257-63. PubMed PMID: 1439601.
145. Egilmez T, Tekin MI, Gonen M, et al. Efficacy and safety of a new-generation shockwave lithotripsy machine in the treatment of single renal or ureteral stones: Experience with 2670 patients. J Endourol. 2007;21(1):23-7. doi: 10.1089/end.2006.0174. PubMed PMID: 17263603.
146. Chua ME, Gatchalian GT, Corsino MV, et al. Diagnostic utility of attenuation measurement (Hounsfield units) in computed tomography stonogram in predicting the radio-opacity of urinary calculi in plain abdominal radiographs. International urology and nephrology. 2012;44(5):1349-55. Epub 2012/05/15. doi: 10.1007/s11255-012-0189-x. PubMed PMID: 22581423.
147. Ather MH, Shrestha B, Mehmood A. Does ureteral stenting prior to shock wave lithotripsy influence the need for intervention in steinstrasse and related complications? Urologia internationalis. 2009;83(2):222-5. doi: 10.1159/000230028. PubMed PMID: 19752621.
148. Tan YM, Yip SK, Chong TW, et al. Clinical experience and results of ESWL treatment for 3,093 urinary calculi with the Storz Modulith SL 20 lithotripter at the Singapore general hospital. Scand J Urol Nephrol. 2002;36(5):363-7. doi: 10.1080/003655902320783872. PubMed PMID: 12487741.
149. Dhar NB, Thornton J, Karafa MT, et al. A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. J Urol. 2004;172(6 Pt 1):2271-4. PubMed PMID: 15538247.
150. Perez Castro E, Osther PJ, Jinga V, et al. Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: the Clinical Research Office of the Endourological Society ureteroscopy global study. European urology. 2014;66(1):102-9. Epub 2014/02/11. doi: 10.1016/j.eururo.2014.01.011. PubMed PMID: 24507782.
151. Drake T, Grivas N, Dabestani S, et al. What are the Benefits and Harms of Ureteroscopy Compared with Shock-wave Lithotripsy in the Treatment of Upper Ureteral Stones? A Systematic Review. European urology. 2017;72(5):772-86. Epub 2017/05/01. doi: 10.1016/j.eururo.2017.04.016. PubMed PMID: 28456350.

152. Rubenstein RA, Zhao LC, Loeb S, et al. Prestenting improves ureteroscopic stone-free rates. J Endourol. 2007;21(11):1277-80. Epub 2007/11/29. doi: 10.1089/end.2007.9888. PubMed PMID: 18042014.

153. Nabi G, Cook J, N'Dow J, et al. Outcomes of stenting after uncomplicated ureteroscopy: systematic review and meta-analysis. BMJ. 2007;334(7593):572. Epub 2007/02/22. doi: 10.1136/bmj.39119.595081.55. PubMed PMID: 17311851; PubMed Central PMCID: PMCPMC1828345.

154. Lingeman JE, Newman D, Mertz JH, et al. Extracorporeal shock wave lithotripsy: the Methodist Hospital of Indiana experience. J Urol. 1986;135(6):1134-7. Epub 1986/06/01. PubMed PMID: 3520015.

155. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28(1):1-13. Epub 2014/02/04. doi: 10.1016/j.idc.2013.09.003. PubMed PMID: 24484571.

156. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 guideline for the management of ureteral calculi. J Urol. 2007;178(6):2418-34. doi: 10.1016/j.juro.2007.09.107. PubMed PMID: 17993340.

157. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest. 2005;115(10):2598-608. Epub 2005/10/04. doi: 10.1172/JCI26662. PubMed PMID: 16200192; PubMed Central PMCID: PMCPMC1236703.

158. Wen CC, Nakada SY. Treatment selection and outcomes: renal calculi. Urol Clin North Am. 2007;34(3):409-19. Epub 2007/08/07. doi: 10.1016/j.ucl.2007.04.005. PubMed PMID: 17678990.

159. Kadlec AO, Greco KA, Fridirici ZC, et al. Comparison of complication rates for unilateral and bilateral percutaneous nephrolithotomy (PCNL) using a modified Clavien grading system. BJU Int. 2013;111(4 Pt B):E243-8. doi: 10.1111/j.1464-410X.2012.11589.x. PubMed PMID: 23106809.

160. Sharma K, Sankhwar SN, Goel A, et al. Factors predicting infectious complications following percutaneous nephrolithotomy. Urol Ann. 2016;8(4):434-8. Epub 2017/01/07. doi: 10.4103/0974-7796.192105. PubMed PMID: 28057987; PubMed Central PMCID: PMCPMC5100148.

161. Zuazu JR, Hruza M, Rassweiler JJ, et al. The Clavien classification system to optimize the documentation of PCNL morbidity. Arch Ital Urol Androl. 2010;82(1):20-2. PubMed PMID: 20593711.

162. Mariappan P, Smith G, Bariol SV, et al. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. J Urol. 2005;173(5):1610-4. Epub 2005/04/12. doi: 10.1097/01.ju.0000154350.78826.96. PubMed PMID: 15821509.

163. Ingimarsson JP, Dagrosa LM, Hyams ES, et al. External validation of a preoperative renal stone grading system: reproducibility and inter-rater concordance of the Guy's stone score using preoperative computed tomography and rigorous postoperative stone-free criteria. Urology. 2014;83(1):45-9. Epub 2013/11/12. doi: 10.1016/j.urology.2013.09.008. PubMed PMID: 24210568.

164. Okhunov Z, Friedlander JI, George AK, et al. S.T.O.N.E. nephrolithometry: novel surgical classification system for kidney calculi. Urology. 2013;81(6):1154-9. Epub 2013/04/02. doi: 10.1016/j.urology.2012.10.083. PubMed PMID: 23540858.

165. Smith A, Averch TD, Shahrour K, et al. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. J Urol. 2013;190(1):149-56. Epub 2013/01/29. doi: 10.1016/j.juro.2013.01.047. PubMed PMID: 23353048.

166. Withington J, Armitage J, Finch W, et al. Assessment of Stone Complexity for PCNL: A Systematic Review of the Literature, How Best Can We Record Stone Complexity in PCNL? J Endourol. 2016;30(1):13-23. doi: 10.1089/end.2015.0278. PubMed PMID: 26414226.

167. Sekar H, Krishnamoorthy S, Kumaresan N, et al. Supracostal Punctures for PCNL: Factors that Predict Safety, Success and Stone Free Rate in Stag Horn and Non-Stag Horn Stones: A Single Centre Experience and Review of Literature. J Clin Diagn Res. 2016;10(9):PC17-PC21. doi: 10.7860/JCDR/2016/21875.8505. PubMed PMID: 27790510; PubMed Central PMCID: PMCPMC5072010.

168. Yang L, Lu S, Han X, et al. Clinical comparison of the efficiency and security of balloon dilators versus fascial dilators in percutaneous nephrolithotripsy (PCNL). Pak J Med Sci. 2016;32(3):635-40. doi: 10.12669/pjms.323.9281. PubMed PMID: 27375705; PubMed Central PMCID: PMCPMC4928414.

169. Thapa BB, Niranjan V. Mini PCNL Over Standard PCNL: What Makes it Better? Surg J (N Y). 2020;6(1):e19-e23. Epub 2020/02/15. doi: 10.1055/s-0040-1701225. PubMed PMID: 32055686; PubMed Central PMCID: PMCPMC7015816.

170. Labate G, Modi P, Timoney A, et al. The percutaneous nephrolithotomy global study: classification of complications. J Endourol. 2011;25(8):1275-80. doi: 10.1089/end.2011.0067. PubMed PMID: 21751882.

171. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13. Epub 2004/07/27. PubMed PMID: 15273542; PubMed Central PMCID: PMCPMC1360123.

172. Folkhälsomyndigheten. Escherichia coli. Resistensläge [Internet] 2017 [cited 2017 2017-12-05]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/sjukdomsstatistik/escherichia-coli/?t=county.

173. Daels FP, Gaizauskas A, Rioja J, et al. Age-related prevalence of diabetes mellitus, cardiovascular disease and anticoagulation therapy use in a urolithiasis population and their effect on outcomes: the Clinical Research Office of the Endourological Society Ureteroscopy Global Study. World J Urol. 2015;33(6):859-64. Epub 2014/08/26. doi: 10.1007/s00345-014-1382-6. PubMed PMID: 25155035.

174. Ichiyanagi O, Nagaoka A, Izumi T, et al. Age-related delay in urinary stone clearance in elderly patients with solitary proximal ureteral calculi treated by extracorporeal shock wave lithotripsy. Urolithiasis. 2015;43(5):419-26. Epub 2015/05/20. doi: 10.1007/s00240-015-0783-3. PubMed PMID: 25981235.

175. Schmidt. Ingrid; Johan Thorb TD, Fredrik Nilsson, Christina Carlssona. The national program on standardized cancer care pathways in Sweden: Observations and findings half way through. Health Policy. 2018;Volume 122, Issue 9, September 2018,(9):Pages 945-8
176. Lindqvist K, Hellstrom M, Holmberg G, et al. Immediate versus deferred radiological investigation after acute renal colic: a prospective randomized study. Scand J Urol Nephrol. 2006;40(2):119-24. doi: 10.1080/00365590600688203. PubMed PMID: 16608809.
177. Rosenlund IM, Forde OH, Revhaug A. Routine deferred computed tomography for patients with suspected urolithiasis is low-value healthcare. Scand J Urol. 2016:1-6. doi: 10.1080/21681805.2016.1254680. PubMed PMID: 27876432.
178. Raskin D, Winkler H, Kleinmann N, et al. Very low-dose computerized tomography for confirmation of urinary stone presence. World J Urol. 2021;39(1):233-8. Epub 2020/03/04. doi: 10.1007/s00345-020-03142-x. PubMed PMID: 32124021.
179. Cornelius J, Zumbuhl D, Afferi L, et al. Immediate Shockwave Lithotripsy vs Delayed Shockwave Lithotripsy After Urgent Ureteral Stenting in Patients with Ureteral or Pyeloureteral Urolithiasis: A Matched-Pair Analysis. J Endourol. 2020. Epub 2020/11/22. doi: 10.1089/end.2020.0384. PubMed PMID: 33218266.
180. Magnusson A, Geterud K, Brekkan E, et al. [Ultrasound vs. CT in ureteral stones--Swedish procedures apply]. Lakartidningen. 2014;111(49-50):2236-7. PubMed PMID: 25584570.
181. Patatas K, Panditaratne N, Wah TM, et al. Emergency department imaging protocol for suspected acute renal colic: re-evaluating our service. Br J Radiol. 2012;85(1016):1118-22. Epub 2012/04/13. doi: 10.1259/bjr/62994625. PubMed PMID: 22496069; PubMed Central PMCID: PMCPMC3587076.
182. Keoghane S, Austin T, Coode-Bate J, et al. The diagnostic yield of computed tomography in the management of acute flank pain and the emergency intervention rate for a proven acute ureteric stone. Ann R Coll Surg Engl. 2018:1-8. Epub 2018/10/06. doi: 10.1308/rcsann.2018.0172. PubMed PMID: 30286646; PubMed Central PMCID: PMCPMC6204509.
183. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. European urology. 2007;52(6):1610-31. Epub 2007/12/13. PubMed PMID: 18074433.
184. Shah M, Naik N, Somani BK, et al. Artificial intelligence (AI) in urology-Current use and future directions: An iTRUE study. Turk J Urol. 2020;46(Supp. 1):S27-S39. Epub 2020/06/02. doi: 10.5152/tud.2020.20117. PubMed PMID: 32479253; PubMed Central PMCID: PMCPMC7731952.
185. Bach C, Karaolides T, Buchholz N. Extracorporeal shock wave lithotripsy: What is new? Arab J Urol. 2012;10(3):289-95. Epub 2012/09/01. doi: 10.1016/j.aju.2012.04.002. PubMed PMID: 26558039; PubMed Central PMCID: PMCPMC4442960.
186. Turan T, Efioglu O, Danacioglu YO, et al. Can intervals in extracorporeal shock wave lithotripsy sessions affect success in the treatment of upper ureteral stones? Wideochir Inne Tech Maloinwazyjne. 2018;13(4):507-11. Epub 2018/12/14. doi:

10.5114/wiitm.2018.75873. PubMed PMID: 30524622; PubMed Central PMCID: PMCPMC6280089.

187. Gokce MI, Akpinar C, Obaid K, et al. Comparison of retrograde ureterorenoscopy (URS) and percutaneous anterograde ureteroscopy for removal of impacted upper ureteral stones >10mm in the elderly population. Int Braz J Urol. 2021;47(1):64-70. Epub 2020/08/26. doi: 10.1590/S1677-5538.IBJU.2019.0638. PubMed PMID: 32840338; PubMed Central PMCID: PMCPMC7712678.
188. Wang Y, Chang X, Li J, et al. Efficacy and safety of various surgical treatments for proximal ureteral stone >/=10mm: A systematic review and network meta-analysis. Int Braz J Urol. 2020;46(6):902-26. Epub 2020/05/28. doi: 10.1590/S1677-5538.IBJU.2019.0550. PubMed PMID: 32459455; PubMed Central PMCID: PMCPMC7527111.
189. Al-Aown A, Kyriazis I, Kallidonis P, et al. Ureteral stents: new ideas, new designs. Ther Adv Urol. 2010;2(2):85-92. Epub 2010/04/01. doi: 10.1177/1756287210370699. PubMed PMID: 21789086; PubMed Central PMCID: PMCPMC3126070.

Paper I

SCANDINAVIAN JOURNAL OF UROLOGY, 2017
https://doi.org/10.1080/21681805.2017.1347821

ORIGINAL ARTICLE

Complications in extracorporeal shockwave lithotripsy: a cohort study

Magnus Wagenius[a,b], Jon Jakobsson[b], Johan Stranne[c] and Adam Linder[a]

[a]Department of Clinical Sciences, Division of Infection Medicine, Lund University, Lund, Sweden; [b]Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden; [c]Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT

Objective: The aim of this study was to evaluate clinically relevant complications within 14 days after extracorporeal shockwave lithotripsy (ESWL) in a modern setting.

Materials and methods: Consecutive ESWL treatments between 2009 and 2015 in Ängelholm Hospital, Sweden, were analyzed retrospectively. The primary outcome was complications in patients seeking medical attention within 14 days after ESWL. Multivariable analysis was used to adjust for confounders such as diabetes, stone size and location, and presence of a urinary stent.

Results: In total, 1838 stones were treated: 1185 (64.4%) localized in the renal pelvis, and 415 (22.5%) in the upper two-thirds and 205 (11.1%) in the lower third of the ureter. Overall, 116 out of 1838 cases (6.4%) needed medical attention within 14 days after ESWL and 75 (4%) crequired hospital care. Infection was found in 44 cases (2.4%), with a positive urine culture in 33 cases. Invasive/operative interventions were performed in 41 cases (2.2%). Distal stones had a lower risk of complications ($p = 0.02$) with ESWL. Diabetes ($p = 0.02$), larger stones (11–20 mm, $p = 0.03$; 21–30 mm, $p = 0.009$) and a need for antiemetics during treatment ($p = 0.02$) were significantly associated with an increased risk of complications.

Conclusions: Few complications are associated with modern ESWL treatment. A frequency of 1 Hz should be used to reduce complications ($p = 0.025$). Diabetes and larger stone size increase the risk of complications. The need for antiemetics during ESWL requires special consideration and further study. Distal stones seem to carry a lower risk of complications ($p = 0.017$).

ARTICLE HISTORY
Received 17 April 2017
Revised 29 May 2017
Accepted 16 June 2017

KEYWORDS
Complications; extracorporeal shockwave lithotripsy; infection; monotherapy; ureteric stone; ureteroscopy

Introduction

The excruciating pain from a kidney stone attack is not an experience you would wish on your worst enemy, and patients will do almost anything to avoid new attacks. Hippocrates specifically mentioned stones in his Hippocratic oath: 'I will not use the knife, not even on sufferers from stone but will withdraw in favor of such men as are engaged in this work'. Despite its long history, we need to learn more about stone disease and its treatment. Stones in the urinary tract are a common clinical problem presenting as pain or infection [1]. Treatment of stones in the urinary tract includes ureteroscopic endoluminal extraction of stones (URS), extracorporeal shockwave lithotripsy (ESWL) and percutaneous nephrolithotripsy (PCNL). The European Association of Urology (EAU) recommends the use of URS and ESWL for removal of ureteric stones. A known complication of ESWL is stone fragments getting stuck in the distal ureter (steinstrasse), which occurs more frequently in patients with larger stones (3–7%) [2,3]. Renal hematoma is the major complication related to renal tissue damage, and is symptomatic in 1–4% of patients [4] and asymptomatic in up to 19–25% [5]. Arrhythmias are not uncommon (1–9%) but are not associated with myocardial damage and severe cardiac events are rare [6]. Case reports of rare complications such as bowel perforation [7] and hepatic hematoma have been published [8]. Infectious complications due to ESWL have been shown to be low (0.7–5.8%) [9] and urosepsis is very low (0.2–1%) [10]. Previously, antibiotic prophylaxis was recommended for all ESWL treatments [11]. However, both the EAU and the American Urological Association (AUA) have changed their guidelines [12] and prophylaxis is now only recommended for diabetic patients and those with ureteral stents/nephrostomy [13]. Bacterial resistance to antibiotics is an increasing problem in Sweden and worldwide [14].

The aim of this study was to evaluate the results from and complications of ESWL treatment, and to identify factors predicting complications of ESWL treatment.

Materials and methods

All 1169 patients treated with ESWL at the Urolithiasis Center at Ängelholm Hospital, in the north-western part of Skåne County, Sweden, during the period 2009–2015 were included. The population of Skåne County is approximately 1.3 million inhabitants (mean age 41 years in 2015). The north-western part of Skåne and the Helsingborg/Ängelholm hospitals serve approximately 450,000 people regarding

CONTACT Magnus Wagenius magnus.wagenius@gmail.com Department of Surgery, Helsingborg Hospital, SE-251 87 Helsingborg, Sweden

Supplemental data for this article can be accessed here.

stone treatment. This study was approved by the local ethics committee at Lund University (Dnr 2016/254).

Stones larger than 6 mm causing obstruction or symptoms were considered a treatment indication. ESWL as treatment modality was decided on by the stone-treating doctor in consensus with the patient. Pre-ESWL stenting was not carried out routinely. Patients received stents owing to obstruction and pain, rarely to stone size alone. All patients were presented with the option of ESWL but patients with stones larger than 6 mm, visualized on plain X-ray [scout picture computed tomography (CT)/plain X-ray] located in the upper two-thirds of the ureter and in the kidney pelvis were recommended ESWL. At the start of the study, plain X-ray was the recommended diagnostic tool; nowadays it has been replaced by CT scan. Data were entered when treating the patients and stored in a computerized medical chart system (Melior).

Data were gathered prospectively, including: age; gender; comorbidities; stones (number; location; size; and side); number of treatments; number of shockwaves; shockwave frequency; Stortz medical lithotripsy index (SMLI); fragmentation; X-ray time; need for contrast; urine dipstick and culture, if needed; pulse, blood pressure and oxygen saturation before and during treatment; stenting; treatment success after 1 month; and the need for acute or other treatment options. Information on clinically significant complications was gathered retrospectively through a systematic review of journals and prescriptions of the patients seeking medical attention within 14 days after ESWL treatment.

Descriptive parameters collected from the medical records are presented in Table 1. As some patients received two treatments at one time and other multiple treatments, the focus was on the number of treatment sessions. EAU guidelines on contraindications for ESWL treatment were used [15]. Stortz Medicals recommendations regarding the number of shockwaves and energy levels were followed. Power ramping was not routinely performed during the study period of ESWL. The ESWL machine used was a Stortz Modulith SLX-F2®. Treatment was given in an outpatient setting. Diabetic patients, patients with a positive urine culture/dipstick and patients with nephrostomy/ureteral stent or catheter were given antibiotic prophylaxis orally approximately 30 min before ESWL [15]. The antibiotic given routinely was ciprofloxacin 500 mg orally as a single-dose regimen, with a few exceptions based on cultures. Intravenously (i.v.) administered alfentanil was used as an analgesic during treatment. Midazolam i.v. was given as a sedative, but was rarely needed, and ondansetron i.v. per weight as an antiemetic. The patient's vital signs (pulse, blood pressure and oxygen saturation) were continuously monitored during the procedure.

Treatment was evaluated after 1 month with a CT scan. Fragmentation was assessed as: 1 = no fragmentation; 2 = partial fragmentation (> 4 mm); 3 = complete fragmentation (< 4 mm); and 4 = total fragmentation (no fragments to be seen). Residual stones were defined by identification on the CT scan. The long-term mortality rate was registered and compared with the Swedish mortality register on 5 December 2016. The first patient was treated in September

Table 1. Descriptive parameters of the patients treated with extracorporeal shockwave lithotripsy (ESWL).

	All treatments ($n = 1838$)
(a) Before ESWL treatment	
Age (years)	
Range	8–93
Median	57
Mean ± SD	57.2 ± 15.6
Gender (male/female)	1193/646
Stent	443 (24.1)
Diabetes	170 (9.2)
(b) During ESWL treatment	
Side	
Right	826 (44.9)
Left	1013 (55.0)
Stone size (mm)	
1–10	1272 (69.1)
11–20	530 (28.8)
21–30	36 (2.0)
No. of stones	
1	1704 (92.6)
2	123 (6.7)
3	12 (0.7)
No. of ESWL treatments	
1	1414 (77.0)
2	347 (19.0)
3	76 (4.0)
4	2 (0.1)
No. of shockwaves	
<3000	285 (15.5)
3000	1504 (82.0)
>3000	33 (1.8)
Antibiotic prophylaxis	
No	1116 (60.7)
Yes	722 (39.2)
Antiemetic	
No	1736 (94.3)
Yes	103 (5.6)
Energy level	
<6	223 (12.1)
6	1083 (58.8)
>6	535 (29.1)
Focus	
Small	1812 (98.4)
Large	27 (1.6)
Fragmentation	
None	32 (1.8)
>4 mm	725 (39.4)
<4 mm	757 (41.4)
Complete	141 (7.7)
Hounsfield units	
0–500	101 (5.5)
500–1000	415 (22.5)
1000–1500	205 (11.1)
>1500	6 (0.3)
Frequency (Hz)	
1	243 (13.2)
1.5	1471 (79.9)
2	105 (1.2)
Contrast given	
No	1812 (98.4)
Yes	27 (1.5)
Stone location	
Renal pelvis	1185 (64.4)
Upper two-thirds of ureter	415 (22.5)
Lower third of ureter	205 (11.1)
Dipstick	
Positive	61(3.3)
Negative	1778 (96.6)
No. of stones	
1	1272 (69.1)
2	530 (28.8)
3	36 (2.0)
(c) After ESWL treatment	
Successful ESWL treatment	
No	512 (27.8)
Yes	1324 (71.9)
Alive	1781
Mortality 90 days	4 (0.2)
Mortality after 90 days	53 (2.9)
Total mortality	57 (3.1)

Data are shown as *n* (%) unless otherwise indicated.

2009 and the last patient in November 2015. Thus, the follow-up time varied between 1 and 7 years.

The reason for admission was defined by the admitting physician, using clinical parameters. To define sepsis, the SEPSIS-3 definitions were used [16]. Values were registered within 72 h of arrival at the hospital [17].

Logistic regression was used to investigate whether significant correlations existed between treatment-associated factors and patients seeking medical attention within 14 days after ESWL treatment. The analyses were compensated for gender and age using SPSS Statistics 24 (IBM Corp., Armonk, NY, USA).

Results

From 2009 to 2015, 1169 patients received treatment in 1838 ESWL sessions. The success rate with ESWL alone was high ($n = 1324$, 71.8%). The locations of treated stones were the renal pelvis ($n = 1185$, 64.4%), upper two-thirds of the ureter ($n = 415$, 22.5%) and lower third of the ureter ($n = 205$, 11.1%). Single treatment was used most frequently ($n = 1414$, 76.7%). The most common complementary treatment was URS ($n = 265$), followed by expectancy/X-ray follow-up ($n = 261$). Most patients did not receive antibiotics ($n = 1116$, 60.7%). Diabetes was present in 170 cases (9.3%) and 443 patients (24%) had stents (double-J or nephrostomy). To visualize the stones, contrast was administered through the nephrostomy tube in 27 patients (1.5%). Data are presented in Table 1. Comparisons between the group with complications ($n = 116$) and all ESWL treatments, with p values, are presented in Table 2.

In 116 out of 1838 cases (sessions) (6.3%), medical attention was sought within 14 days of ESWL treatment. A flowchart of included patients and the various subgroups is shown in Figure 1. Of the 116 patients who sought medical attention, microbiological agents were found in cultures in 33 cases. *Escherichia coli* was the most common agent, found in 11 out of 1838 cases (0.6%). The microbiological agents found in cultures and their resistance patterns are presented in supplementary Table S1.

Of the 1838 ESWL treatments, admission for hospital care was needed in 75 cases (4%). The mean length of hospital stay was 2.4 days (range 1–13 days). Overall, infection was found in 36 cases (1.9%). Intravenous antibiotics were administered as treatment in 22 (1.2%) of the treatment sessions. Forty-four patients (2.4% of cases) sought medical attention because of infection. The admission rate was 2% (36/1838) and seven of the patients had sepsis; none of the patients with sepsis had an infection with a microbial agent resistant to the antibiotic given as prophylaxis before ESWL treatment.

Stones 21–30 mm in size ($p = 0.012$, odds ratio = 3.317) and diabetes ($p = 0.009$, odds ratio = 2.106) increased the risk of complications (Table 3). Of the 47 patients admitted for non-infectious reasons, the main cause was obstructive pain and uropathy, and 41 patients (2.2% of cases) underwent an operation. An additional 24 patients (1.3%) were admitted for various reasons such as hematuria, chest pain, stroke and various other non-urological, non-infectious reasons. These findings are further described in Table 3. The complications are grouped according to Clavien–Dindo grade in Table 4.

The overall long-term mortality during the study period was recorded in 57 patients. All 1169 patients had a follow-up time in terms of mortality of at least 1 year. At the 3, 5 and 7 year follow-up, 916, 598 and 96 patients, respectively, were available for evaluation. There were no in-hospital deaths and no patients were admitted to the intensive care unit. Four out of the 57 patients (7%) died within 90 days of ESWL treatment. The cases were inspected and none of the deaths was considered to be linked to ESWL treatment. There was no difference in mortality between patients with and those without complications from ESWL.

Discussion

The modern method of treating urinary stones with ESWL has reduced complications in general, compared to previous treatment procedures and machines. The outpatient procedure, including light sedation (not full anesthesia) and the modern ESWL machines (generations 3 and 4) provide easier ways to follow and focus on the stone. They are versatile, user friendly and highly efficient, with sustained safety. This large single-center study had a stone-free rate (SFR) of 71.8%, which is comparable to other studies [18,19]. Patients with significant complications after ESWL were identified. The main findings are that stone size, diabetes, higher energy level and the use of antiemetics increase the risk of clinically significant complications, and that treatment of distal stones seems to have a lower risk of complications. Pain and infection are the major reasons for seeking medical aid. The complication rate (seeking medical aid within 14 days after treatment) in this study was 6.3% (116/1838). This is in line with Jagtap et al., who found a total complication rate of 5.9% (298/5017) [20]. The morbidity rate and hospital admission rates in similar studies vary between 2.9% and 38.7% [21,22].

When discussing infection, the EAU guidelines note the risk of bacteriuria as being 7–23%. The EAU guidelines state: 'No standard antibiotic prophylaxis before SWL/ESWL is recommended'; prophylaxis is recommended in cases of internal stenting and those with increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, infectious stones or bacteriuria) [12,23]. In the present study, there was a significant correlation between bacteriuria/positive dipstick and the risk of complications ($p = 0.005$). All patients in this study with EAU risk factors were given a single dose of ciprofloxacin. The rate of infectious complications was 2.4% (44/1838). Mira Moreno et al. found a rate of 1.2% symptomatic urinary infections in 366 patients [9]. They gave no antibiotics to the 64 stented patients (17.5%) or 38 diabetics, but all patients were negative on culture preoperatively. In the present study, infectious complications were relatively common. Stones are often colonized with bacteria [24], and it may be assumed that the proportion of bacteria is correlated to stone size and maybe also to the risk of infectious complications. The sepsis rate in this study was 0.4% (7/1838); other studies show a rate of 0–0.6% [20,22] and EAU guidelines note the risk of

Table 2. Comparison between ESWL parameters and the risk of having a complication.

Variable	*n* (missing)	*p* (variable)	Comparison	OR (95% CI)	*p* (OR)
Gender	1838 (1)	0.4722			
1: Male			2 vs 1	1.17 (0.77–1.78)	0.4722
2: Female					
Age	1838 (1)	0.3986	Continuous	0.99 (0.98–1.01)	0.3986
No. of shockwaves	1820 (19)	0.6218	Continuous	1.00 (1.00–1.00)	0.6218
Shockwaves	1820 (19)	0.1663			
1: < 3000			2 vs 1	0.82 (0.49–1.39)	0.4630
2: 3000			3 vs 1	2.00 (0.69–5.84)	0.2024
3: > 3000					
Antibiotics	1838 (1)	0.5351			
0: No			1 vs 0	1.14 (0.75–1.74)	0.5351
1: Yes					
Antiemetics	1838 (1)	0.0167			
0: No			1 vs 0	2.25 (1.16–4.38)	0.0167
1: Yes					
Diabetes	1838 (1)	0.0204			
0: No			1 vs 0	2.04 (1.12–3.74)	0.0204
1: Yes					
Energy level	1817 (22)	0.0072	Continuous	0.80 (0.68–0.94)	0.0072
Focus	1838 (1)	0.6684			
0: Small			1 vs 0	0.72 (0.16–3.27)	0.6684
1: Large					
Fragmentation: grouped	1653 (186)	0.0514			
1: None			2 vs 1	0.37 (0.13–1.09)	0.0707
2: ≥ 4 mm			3 vs 1	0.54 (0.19–1.59)	0.2643
3: < 4 mm			4 vs 1	0.84 (0.26–2.77)	0.7778
4: Complete					
Hounsfield units	727 (1112)	0.4177			
1: 0–500			2 vs 1	2.26 (0.65–7.88)	0.1998
2: 500–1000			3 vs 1	1.87 (0.50–7.05)	0.3537
3: 1000–1500			4 vs 1	6.24 (0.55–70.36)	0.1384
4: > 1500					
Frequency	1818 (21)	0.0470			
1: 1 Hz			2 vs 1	2.14 (1.10–4.16)	0.0249
2: 1.5 Hz			3 vs 1	1.15 (0.36–3.70)	0.8107
3: 2 Hz					
Stone location	1804 (35)	0.0340			
0: Renal pelvis			1 vs 0	0.68 (0.39–1.18)	0.1755
1: Upper ureter			2 vs 0	0.30 (0.11–0.81)	0.0169
2: Lower ureter					
Dipstick	1838 (1)	0.0052			
0: Negative			1 vs 0	2.86 (1.37–5.99)	0.0052
1: Positive					
SMLI	1746 (93)	0.5605	Continuous	1.00 (1.00–1.00)	0.5605
Stone location	1838 (1)	0.9877			
Right side			2 vs 1	1.00 (0.66–1.53)	0.9877
Left side					
No. of stones	1838 (1)	0.0478			
1			2 vs 1	2.40 (1.13–5.10)	0.0223
2			3 vs 1	1.81 (0.85–3.86)	0.1232
3					
Stone size	1837 (2)	0.0069			
1: 1–10 mm			2 vs 1	1.54 (1.05–2.26)	0.0283
2: 11–20 mm			3 vs 1	3.59 (1.38–9.33)	0.0089
3: 21–30 mm					
Stent	1838 (1)	0.6535			
0: No			1 vs 0	0.89 (0.53–1.50)	0.6535
1: Yes					

All values are adjusted for gender and age.
OR: odds ratio; SMLI: Stortz medical lithotripsy index (total energy administered).

sepsis to be 1–2.7%. The most frequent complication in this study was pain, in 66 out of 1838 cases (3.6%). Surgery was needed in 41 cases (2.2%) owing to obstruction, infections and pain, which is in line with the rate of 1.7% found by Jagtap et al. [20]. Hospital admission was required in 75 out of 1838 cases in the present study (4%), which is slightly higher the admission rate of 2.9% reported by Tan et al. [22]. Stenting is recommended for larger stones than 20 mm [25] and it could increase the SFR [26]. α-Blockers have been suggested to be beneficial and to reduce stent-related symptoms, including pain [27]. The indications for stenting in the present study were obstruction and pain, and more rarely stone size, since stenting also has disadvantages [28]. The present data indicate that stenting could be considered when stones are larger than 10 mm. Diabetes has been shown to be a risk factor for infection after ESWL treatment [13]. Diabetes is mostly mentioned as a late 'complication' in association with ESWL. A strong association was found between clinically significant complications and diabetes ($p = 0.002$), and diabetic patients consume more healthcare

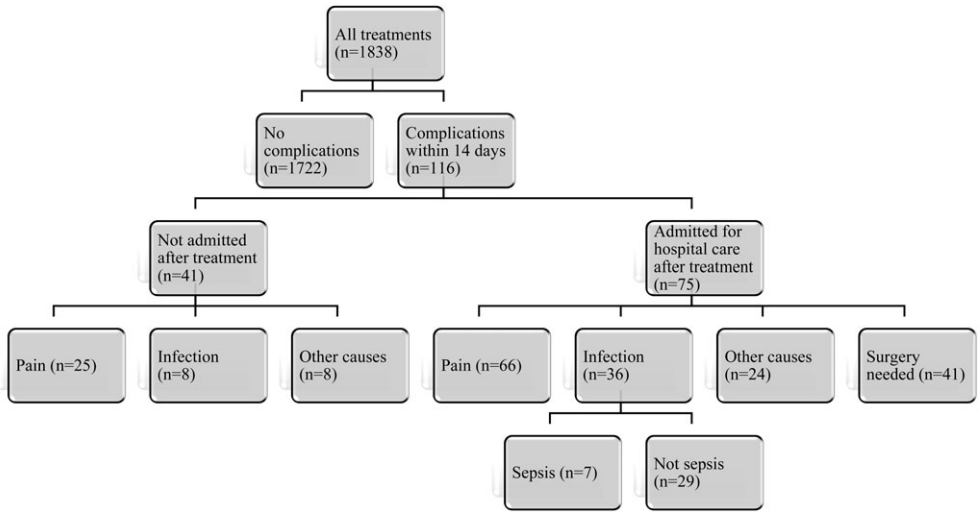


Figure 1. Flowchart of all the treatments and the subgrouping used in the study.

Table 3. Complications with regard to diabetes and stone size.

		Diabetes		Stone size (mm)		
Complication	Total ($n = 116$)	Yes ($n = 18$)	No ($n = 98$)	1–10 ($n = 69$)	11–20 ($n = 41$)	21–30 ($n = 6$)
Infection	36 (31.0)	6 (33.3)	30 (30.6)	17 (24.6)	16 (39.0)	3 (50.0)
Kidney hematoma	6 (5.2)	1 (5.6)	5 (5.1)	5 (7.2)	1 (2.4)	0 (0.0)
Surgery	41 (35.3)	7 (38.9)	30 (30.6)	22 (31.9)	13 (31.7)	2 (33.3)
Pain	66 (56.9)	10 (55.6)	56 (57.1)	43 (62.3)	21 (51.2)	2 (33.3)
Admitted	75 (64.6)	12 (66.7)	62 (63.3)	46 (66.7)	25 (61.0)	3 (50.0)
Other causes	18 (15.5)	1 (5.6)	17 (17.4)	12 (17.4)	5 (12.2)	1 (16.7)

Data are shown as number of treatments with this complication (%) in this group. Treatment can lead to more than one complication.

Table 4. Complications group according to Clavien–Dindo grade.

Variable	No. of patients per treatment (%)
Complications (Clavien–Dindo grade)	116 (6.3)
Grade I	
Fever	9 (0.59)
Renal colic/pain/other causes	33 (1.8)
Grade II	
Pain (admitted, not operated)	29 (1.6)
Renal hematoma	6 (0.3)
Grade IIIa	
Obstruction (relieved by percutaneous nephrostomy)	8 (0.4)
Grade IIIb	
Obstruction (relieved by double-J stenting)	15 (0.8)
Steinstrasse (relieved by double-J stenting URS)	16 (0.9)
Grade IV	
Urosepsis	7 (0.4)

URS: ureteroscopic endoluminal extraction of stones.

resources than the general population. Sugar leakage in the urine may contribute to a higher risk of infectious complications. Recommending general intravenous antibiotics for these groups (i.e. patients with stents and/or diabetes) may be taking it too far, but optimizing diabetic treatment, performing urine culture and considering antibiotic treatment must be contemplated. The microbiological agents found in cultures reflect the authors' clinical experience of urological infections, with 33% being caused by *E. coli*. The increasing resistance of *E. coli* is alarming [14] and infectious complications in the future will be very challenging.

A correlation was found between the energy level and the risk of complications ($p = 0.007$). Complications increased when patients received antiemetics ($p = 0.017$), possibly owing to the greater use of analgesics. Whether this is because of an underlying complication such as tissue damage, hematoma or obstruction, or because these patients are more sensitive to pain, is not known and needs further study. A frequency of 1.5 Hz compared to 1 Hz also proved to be a risk factor for complications ($p = 0.025$). Previous studies have shown that the optimal frequency for increased SFR is 1–1.5 Hz [29,30]. It may be worth taking the extra time to reduce the frequency to 1 Hz if it reduces the complication rates. Stones in the distal ureter had significantly fewer complications ($p = 0.017$) than kidney stones. The authors usually recommend URS and laser treatment for these stones, and the risk reduction seen may be due to selection bias in choosing patients for ESWL compared to surgery. In this study, the stented group was not more prone to infectious complications ($p = 0.63$) and there was no correlation between age and infection, in contrast to the findings of Mira Moreno et al. [9]. Stone treatment could be improved by giving patients access to a special 'stone nurse'.

Standardizing which variables to consider is a necessity for better evaluation of results and complications. Selection of the most suitable patients for ESWL can be achieved using simple parameters such as stone volume, Hounsfield units and the distance from the energy source to the stone, measured as skin-to-stone distance. Addressing complications is a complex task, involving many parameters. Grading can be kept simple by using the established Clavien–Dindo system used by Jagtap et al. [20].

Patients with known risk factors were given antibiotic prophylaxis in accordance with recommendations [13] in this study, which probably kept the infectious complication rate down. Despite this, 0.4% of cases developed sepsis. The definition of sepsis differs between studies and is not always clear. None of the other studies used the sequential organ failure assessment (SOFA) score, which is supposed to measure a dysregulatory host response to infection. An elevated creatinine level could be due to obstructive uropathy in this study and is a substantial confounder.

When presenting large patient numbers, the risk of human error increases. Other comorbidities, such as hypertension and anticoagulants, could have an effect on the complications and results, and the American Society of Anesthesiologists score and Charlson comorbidity index were not registered. Not all patients were treated with α-blockers, and non-steroidal anti-inflammatory drugs were recommended as painkillers only when needed. There was a lack data on Hounsfield units in up to 60% of the cases. Data regarding other parameters were acceptable. When measuring stone size, there is always the risk of incorrect measurements, although this risk has been reduced by the more frequent use of CT. This study included all patients treated with ESWL for urological stones at the Urolithiasis Center at Ängelholm Hospital between 2009 and 2015. Selection and exclusion of some patients would be preferred as this would increase the SFR results, but the authors chose to present the whole group. It is likely that frail, elderly patients with more comorbidities were chosen for ESWL treatment to a greater extent. Comparative studies of ESWL, URS and PCNL, preferably randomized, are needed to investigate this. The authors aim to conduct comparable studies of URS and PCNL (during the same timeframe, 2009–2015) in their center.

This is a large Swedish study addressing clinically significant complications of ESWL treatment. It provides an update in the field of stone management in a modern setting. As in many other studies, it can be concluded that ESWL is a good treatment option with a high SFR and low complication rate. The data indicate that 1.5 Hz (instead of 1 Hz), diabetes and stones larger than 10 mm increase the risk of complications, and such patients need special consideration before treatment. Patients in need of antiemetics during treatment deserve special consideration during follow-up. Distal stones have a lower risk of complications after ESWL but the complication rate after URS is not known. Decreasing the frequency of shockwave administration to 1 Hz may reduce complications; this is a little more time consuming but still results in a good SFR. Patients need to be advised before treatment with ESWL if they have an increased risk of complications, and easy ways to detect complications need to be established.

Acknowledgements

We would like to thank the staff at the Department of Urology, Ängelholms Hospital, for helping with patient registration.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Gorthon Foundation, Lions Foundation, Percy Falk Foundation and ALF Region Skåne.

ORCID

Magnus Wagenius http://orcid.org/0000-0002-4004-269X
Jon Jakobsson http://orcid.org/0000-0001-7408-4372
Johan Stranne http://orcid.org/0000-0002-4295-6524
Adam Linder http://orcid.org/0000-0002-8187-7239

References

[1] Elton TJ, Roth CS, Berquist TH, et al. A clinical prediction rule for the diagnosis of ureteral calculi in emergency departments. J Gen Intern Med. 1993;8:57–62.
[2] Lucio J, 2nd, Korkes F, Lopes-Neto AC, et al. Steinstrasse predictive factors and outcomes after extracorporeal shockwave lithotripsy. Int Braz J urol. 2011;37:477–482.
[3] Tomescu P, Panus A, Mitroi G, et al. Assessment of extracorporeal shock wave lithotripsy (ESWL) therapeutic efficiency in urolithiasis. Curr Health Sci J. 2009;35:40–43.
[4] Dhar NB, Thornton J, Karafa MT, et al. A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. J Urol. 2004;172:2271–2274.
[5] Telegrafo M, Carluccio DA, Rella L, et al. Diagnostic and prognostic role of computed tomography in extracorporeal shock wave lithotripsy complications. Urol Ann. 2016;8:168–172.
[6] Eaton MP, Erturk EN. Serum troponin levels are not increased in patients with ventricular arrhythmias during shock wave lithotripsy. J Urol. 2003;170:2195–2197.
[7] Holmberg G, Spinnell S, Sjodin JG. Perforation of the bowel during SWL in prone position. J Endourol. 1997;11:313–314.
[8] Kim TB, Park HK, Lee KY, et al. Life-threatening complication after extracorporeal shock wave lithotripsy for a renal stone: a hepatic subcapsular hematoma. Korean J Urol. 2010;51:212–215.
[9] Mira Moreno A, Montoya Lirola MD, Garcia Tabar PJ, et al. Incidence of infectious complications after extracorporeal shock wave lithotripsy in patients without associated risk factors. J Urol. 2014;192:1446–1449.
[10] Muller-Mattheis VG, Schmale D, Seewald M, et al. Bacteremia during extracorporeal shock wave lithotripsy of renal calculi. J Urol. 1991;146:733–736.
[11] Pearle MS, Roehrborn CG. Antimicrobial prophylaxis prior to shock wave lithotripsy in patients with sterile urine before treatment: a meta-analysis and cost-effectiveness analysis. Urology. 1997;49:679–686.
[12] Lu Y, Tianyong F, Ping H, et al. Antibiotic prophylaxis for shock wave lithotripsy in patients with sterile urine before treatment may be unnecessary: a systematic review and meta-analysis. J Urol. 2012;188:441–448.
[13] European Association of Urology. Urolithiasis [Online]. 2016. Available from: http://uroweb.org/guideline/urolithiasis/.
[14] Folkhälsomyndigheten. E. coli Resistensläge [Online]. 2016 [Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/sjukdomsstatistik/escherichia-coli/?t=com&p=6156.

[15] Assimos DG. Re: EAU guidelines on interventional treatment for urolithiasis. J Urol. 2016;195:659
[16] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–810.
[17] Williams JM, Greenslade JH, McKenzie JV, et al. SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection. Chest. 2017;151:586–596.
[18] Tiselius HG, Ackermann D, Alken P, et al. Guidelines on urolithiasis. Eur Urol. 2001;40:362–371.
[19] Torricelli FC, Danilovic A, Vicentini FC, et al. Extracorporeal shock wave lithotripsy in the treatment of renal and ureteral stones. Rev Assoc Med Bras (1992). 2015;61:65–71.
[20] Jagtap J, Mishra S, Bhattu A, et al. Evolution of shockwave lithotripsy (SWL) technique: a 25-year single centre experience of >5000 patients. BJU Int. 2014;114:748–753.
[21] Al-Marhoon MS, Shareef O, Al-Habsi IS, et al. Extracorporeal shock-wave lithotripsy success rate and complications: initial experience at Sultan Qaboos University Hospital. Oman Med J. 2013;28:255–259.
[22] Tan YM, Yip SK, Chong TW, et al. Clinical experience and results of ESWL treatment for 3,093 urinary calculi with the Storz Modulith SL 20 lithotripter at the Singapore general hospital. Scand J Urol Nephrol. 2002;36:363–367.
[23] Honey RJ, Ordon M, Ghiculete D, et al. A prospective study examining the incidence of bacteriuria and urinary tract infection after shock wave lithotripsy with targeted antibiotic prophylaxis. J Urol. 2013;189:2112–2117.
[24] Marien T, Miller NL. Treatment of the infected stone. Urol Clin North Am. 2015;42:459–472.
[25] Sulaiman MN, Buchholz NP, Clark PB. The role of ureteral stent placement in the prevention of Steinstrasse. J Endourol. 1999;13:151–155.
[26] Assimos D, Crisci A, Culkin D, et al. Preoperative JJ stent placement in ureteric and renal stone treatment: results from the Clinical Research Office of Endourological Society (CROES) ureteroscopy (URS) Global Study. BJU Int. 2016;117:648–654.
[27] Dellis AE, Keeley FX Jr, Manolas V, et al. Role of alpha-blockers in the treatment of stent-related symptoms: a prospective randomized control study. Urology. 2014;83:56–61.
[28] Musa AA. Use of double-J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. Int Urol Nephrol. 2008;40:19–22.
[29] Ahuja M, Goel A. Re: Yilmaz E, Batislam E, Basar M, et al: Optimal frequency in extracorporeal shock wave lithotripsy: prospective randomized study (Urology 66: 1160-1164, 2005). Urology. 2008;71:354. author reply 5.
[30] Li K, Lin T, Zhang C, et al. Optimal frequency of shock wave lithotripsy in urolithiasis treatment: a systematic review and meta-analysis of randomized controlled trials. J Urol. 2013;190:1260–1267.

Paper II

ORIGINAL PAPER

UROLITHIASIS

Ureteroscopy: a population based study of clinical complications and possible risk factors for stone surgery

Magnus Wagenius[1,2], Mattias Rydberg[1], Marcin Popiolek[3], Andreas Forsvall[1], Johan Stranne[4], Adam Linder[2]

[1]Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden
[2]Department of Clinical Sciences, Division of Infection Medicine, Lund University, Lund, Sweden
[3]Department or Urology, Örebro University Hospital, Örebro, Sweden
[4]Department of Urology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[5]Region Västra Götaland, Sahlgrenska University Hospital, Department of Urology, Gothenburg, Sweden

Citation: Wagenius M, Rydberg M, Popiolek M, Forsvall A, Stranne J, Linder A. Ureteroscopy: a population based study of clinical complications and possible risk factors for stone surgery. Cent European J Urol. 2019; 72: 285-295.

Article history
Submitted: May 3, 2019
Accepted: Aug. 22, 2019
Published online: Sept. 2, 2019

Corresponding author
Magnus Wagenius
Lund, Helsingborg Hospital
Department of Urology
3-5 Svartbrödragränden
25187 Helsingborg, Sweden
phone: +46 708 182 864
magnus.wagenius@med.lu.se

Introduction The aim of this study was to describe the complications of ureteroscopy (URS) and to investigate whether performing URS outside normal working hours leads to increased risk for clinically significant complications.

Material and methods A cohort of 486 consecutive patients treated with URS, with a total of 567 sessions between 2009 and 2015 at Helsingborg/Ängelholm Hospital, Sweden, was analyzed. Outcome was complications within 14 days after URS treatment.

Results We found no increased risk of complications related to URS performed outside normal working hours. Stone-free rate (SFR) in the distal third of the ureter was 95.2% (315/331), in the middle ureter 92.8% (90/97), in the proximal ureter 84.0% (63/75) and 69.0% (40/58) in renal pelvis. The overall complication rate was 10.6% (n = 60). None of the potential risk factors for complications showed any significance when adjusted for age and gender. We found an inverse relationship between stenting and SFR (p = 0.002). The most common preoperatively cultured bacteria was Escherichia coli. With adequate antibiotics, there was no increased risk of complications. There was an increased risk of complications after URS related to age, but not with gender.

Conclusions URS in modern setting provides excellent results with adequate SFR and low morbidity. Time of day, the presence of urological specialized operating nurses did not affect the risk of complications and we found no other significant risk factors for complications. Escherichia coli was the most commonly found bacteria in preoperative cultures. The risk of complications increases with age. For patients >65 years old, this should be considered in preoperative counseling.

Key Words: complications ‹› infection ‹› monotherapy ‹› ureteric stone ‹› ureteroscopy ‹› stone

INTRODUCTION

For the past 7,000 years our civilizations have been trying to find a cure to the suffering caused by stones in the urinary tract [1]. We can now treat stones within the urinary tract, and minimize the morbidity and mortality. In Sweden, the incidence of urolithiasis is 1–2% in males and 0.5% in females [2]. The prevalence was over 10% in males and 3% in females. The recurrence of urolithiasis within 10 years has been reported to be 26% in first-time stone formers [3]. The prevalence of urolithiasis in Western countries range from 8-19% in males and from 3–5% in females [4] and the prevalence of urolithiasis is increasing [5].

Studies suggest that ureteroscopy (URS) is as effective as extracorporeal shockwave lithotripsy (ESWL) for treating stones also in proximal parts of the urinary tract [6, 7]. The guidelines of the European Association of Urology (EAU) [8] recommend using

either ESWL or URS for stones <2 cm. With the exception of untreated urinary tract infections (UTI) and contraindications for general anesthesia, URS can be safely performed in the majority of patients. The Holmium: YAG laser is effective on all types of stones and is nowadays considered the gold standard for stone disintegration. Preoperative stenting has been shown to increase the success rate of the URS treatment [9]. The usage of postoperative stents in URS can, however, cause irritative lower urinary symptoms [10].

Stone-free rate (SFR) is used to measure outcome and successful treatment. Residual stones ≤4 mm in diameter after treatment have been considered clinically insignificant, and the patient considered stone- free [11]. The complication rates range from 9–25%, after URS [8].

A urine culture is mandatory according the EAU guidelines, and patients with a UTI should receive antibiotic treatment prior to URS [8]. The most common bacteria causing a UTI is Escherichia coli [12]. The complication rates for post-URS UTI range from 2–4%, and the rates of sepsis range from 2–4% [13].

The discussion of whether stone surgery should be done outside normal working hours or not is debated within the urological society. The influence of personnel not specially trained in urological procedures (on- call operating personnel) and whether the surgeon's fatigue may affect outcome and complication rates is debated and sometimes used as an excuse for not preforming stone surgery at night.

The objective of this study is to retrospectively evaluate the outcome of patients treated with URS in the north-western part of the Scania County, Sweden, during the period of 2009 to 2015. Additionally, our goal was to describe the complication's related to URS. Evaluating and understanding the complications may potentially lead to better patient selection and consequently improved safety for patients treated with URS.

MATERIAL AND METHODS

All consecutive patients treated with URS at Helsingborg/Ängelholm Hospital in the north-western part of Scania County, Sweden, during the period 2009–2015, were included. Symptomatic stones >6 mm were considered a treatment indication. Stones <6 mm persisting after one month on X-ray were also considered a treatment indication.

The method used to treat the stone was decided by the urologist in consensus with the patient. Patients with stones >6 mm and located in the lower third part of the ureter were recommended URS. Pre-URS stenting was not used routinely.

A semi-rigid ureteroscope was used when the stone was located in the ureter. A flexible ureteroscope was used in the renal pelvis. Holmium Laser was used for fragmentation.

For the journal search the Swedish surgical codes for nephro-pyelo-lithotomy, urethero-lithotomy, and uretheroscopy were used, also including the diagnoses in the updated Charlson Comorbidity Index and mortality [14] (see Appendix 1).

The data gathered were: sex; age at intervention; size and location of stones according to pre- and postoperative computed tomography (CT) scan; pre- and postoperative use of pigtail stent; preoperative urine culture; type of bacteria; pre-, per-, and postoperative antibiotics; days with antibiotics; days of hospitalization; and if the patient sought medical attention at the emergency department within 14 days of the surgery.

Stone-free status was defined as absence of stones or presence of residuals ≤4 mm, in accordance with the clinic standard, evaluated on postoperative CT, and presented as: no residual stones, residual stones ≤2 mm, and residual stones ≤4 mm. If the urologist during the operation could confirm that all stones and fragment were removed, it was not mandatory to follow-up with a CT. For patients without a follow-up CT, the medical records were re-examined ensuring that the patient had not sought medical attention due to stone events within one year after the treatment. To evaluate if the complication rate could correlate to the personnel performing surgery (on-call personnel/normal operating personnel), if fatigue could be a factor (nights, not between 0800-1700) or if surgery was performed acute or elective could have an effect on complications, data was collected from the surgical procedures. Additionally, flexible and semi-rigid ureteroscopy were compared regarding the complication rates.

To grade surgical complications, a modified version of the Clavien-Dindo classification was used (see Appendix 2). The classification can be used in all types of surgery [15].

For patients registered at the emergency department within 14 days, further data were extracted: cause of admission decided by the admitting doctor (infection, bleed, pain, or other); days until readmission; if the patient was readmitted; days of re-hospitalization; if blood and/or urine cultures were taken; type of bacteria; antibiotics given; ICU treatment; respiratory rate; level of consciousness; and if the systolic blood pressure were below 100 mmHg.

Registration of the long-term mortality was made on December 12, 2017, ranging from 3 to 9 years. The mortality was reviewed and registered at fixed intervals following the URS treatment; at 28 days,

Table 1. *Patient characteristics and complications*

		All patients (n = 567)	Patients not seeking medical within 14 days (n = 507)	Patients seeking medical care within 14 days (n = 60)
Age, Mean (±SD)		55.0 (16.3)	54.8 (16.1)	56.7 (18.1)
Diabetes		12.2% (n = 69)	12.4% (n = 63)	10.0% (n = 6)
Sex M:F ratio		2.5:1	2.6:1	2:1
Charlson Comorbidity Index	0	71.4% (n = 405)	72.0% (n = 365)	66.7% (n = 40)
	1	6.2% (n = 35)	5.5% (n = 28)	11.7% (n = 7)
	2	15.9% (n = 90)	15.4% (n = 78)	20.0% (n = 12)
	3	3.9% (n = 22)	4.1% (n = 21)	1.7% (n = 1)
	4	1.6% (n = 9)	1.8% (n = 9)	–
	6	0.4% (n = 2)	0.4% (n = 2)	–
	7	0.2% (n = 1)	0.2% (n = 1)	–
	8	0.5% (n = 3)	0.6% (n = 3)	–
Mortality	28-d	–	–	
	90-d	0.2% (n = 1)	–	1.7% (n = 1)
	1y	0.9% (n = 5)	0.8% (n = 4)	1.7% (n = 1)
	2y	2.1% (n = 12)	2.0% (n = 10)	3.3% (n = 2)
	3y	2.8% (n = 16)	2.6% (n = 13)	5.0% (n = 3)
	5y 8y	4.8% (n = 27)	5.1 % (n = 26)	5.0% (n = 3)
		6.0% (n = 34)	5.9 % (n = 30)	6.7% (n = 4)
Clavien-Dindo Classification Score	0	79.4% (n = 450)	87.2% (n = 442)	13.3% (n = 8)
	1	12.0% (n = 68)	9.9% (n = 50)	30.0% (n = 18)
	2	6.5% (n = 37)	2.2% (n = 11)	43.3% (n = 26)
	3	1.9% (n = 11)	0.8% (n = 4)	11.7% (n = 7)
	4	0.2% (n = 1)	–	1.7% (n = 1)

90 days, 1 years, 2 years, 3 years, 5 years, and 8 years.

Statistical methods

For correlations between different variables, univariate logistic regression analyses were used. If the analyses were found to be statistically significant, multivariate logistic regression was used comparing the multiple covariates to the same dependent. When the multivariate logistic regression analysis was used, gender and age were included as predefined confounding variables. In case of a small sample (n <10/covariate) no multivariate logistic regression analysis was used. When comparing non-binary variables, the Kruskal-Wallis test was used. The value of $p < 0.05$ was considered statistically significant. The statistical analyses were performed using IBM SPSS for Mac OS v24.0.0.0.

This study was approved by the local ethics committee at Lund University (Dnr 2017/15) and the head of the Department of Urology at Helsingborg Hospital.

RESULTS

Between January 2009 and December 2015, 486 individual patients were treated with URS in a total of 567 sessions. In 60.4% (343/568) the patients could be discharged from the hospital on the same day. If admitted the mean hospitalization time was 2.0 days. 81 (14.3%) patients demanded multiple sessions, whereas 28 (4.9%) of the patients were treated two times, five patients were treated three times, and two patients were treated five times. Twenty patients (3.5%) were re- treated for the same stone within 6 months.

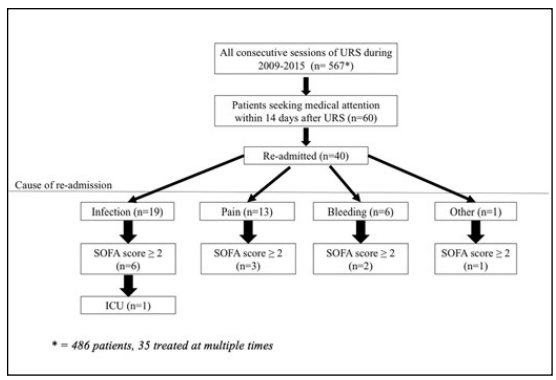


Figure 1. *Flowchart of re-admitted patients, divided into cause of re-admission. The distribution of patients with sequential sepsis-related organ failure assessment (SOFA) score ≥ is also shown.*

Table 2. *Stone characteristics and use of ureteral stent*

		All patients (n = 567)	Patients not seeking medical care within 14 days (n = 507)	Patients seeking medical care within 14 days (n = 60)
Stone location	Distal	58.4% (n = 331)	58.4% (n = 296)	58.3% (n = 35)
	Middle	17.1% (n = 97)	17.9% (n = 91)	10.0% (n = 6)
	Proximal	13.2% (n = 75)	13.2% (n = 67)	13.3% (n = 8)
	Renal pelvis	10.2% (n = 58)	9.5% (n = 48)	16.7% (n = 10)
	Bilateral	1.1% (n = 6)	1.0% (n = 5)	1.7% (n = 1)
Stone size	≤2 mm	1.8%(n = 10)	1.6% (n = 8)	3.3% (n = 2)
	>2≤4 mm	18.0% (n = 102)	18.1% (n = 92)	16.7% (n = 10)
	>4-≤6 mm	32.3% (n = 183)	33.2% (n = 168)	25.0% (n = 15)
	>6≤10 mm	40.2% (n = 228)	39.3% (n = 199)	48.3% (n = 29)
	>10 mm	7.7% (n = 44)	7.9% (n = 40)	6.7 (n = 4)
Stone size at follow-up	No residual stones	59.8% (n = 339)	59.2% (n = 300)	65.0% (n = 39)
	≤2 mm	3.5% (n = 20)	3.4% (n = 17)	5.0% (n = 3)
	>2≤4 mm	3.2% (n = 18)	2.4% (n = 12)	10.0% (n = 6)
	>4-≤6 mm	5.8% (n = 33)	5.6% (n = 28)	8.4% (n = 5)
	>6≤10 mm	2.8%(n = 16)	3.0% (n = 15)	1.7% (n = 1)
	>10 mm	1.1% (n = 6)	1.0% (n = 5)	1.7% (n = 1)
	No follow-up	21.7% (n = 123)	23.5% (119)	6.7% (n = 4)
	Patient no-show	1.9% (n = 11)	2.0% (n = 10)	1.7% (n = 1)
	No longer in Scania	0.2% (n = 1)	0.2% (n = 1)	–
Ureteral stent	Before	15.9% (n = 90)	15.8% (n = 80)	16.7% (n = 10)
	After	34.4% (n = 195)	34.3% (n = 174)	35.0% (n = 21)
SFR		90.7 (n = 515)	90.3% (n = 458)	88.3% (n = 53)

SFR – stone-free rate

Table 3a. *Preoperative stone location in the upper urinary tract and residual stone size*

	Distal third of ureter (n = 331)	Middle third of ureter (n = 97)	Proximal third of ureter (n = 75)	Renal pelvis (n = 58)
SFR	95.2% (n = 315)	92.8% (n = 90)	84.0% (n = 63)	69.0% (n = 40)
No residual stones	66.2% (n = 219)	62.9% (n = 61)	50.7% (n = 38)	34.5% (n = 20)
≤2 mm	2.7% (n = 9)	4.2% (n = 4)	5.3% (n = 4)	5.1% (n = 3)
>2 ≤4 mm	0.9% (n = 3)	3.1% (n = 3)	6.7% (n = 5)	10.4% (n = 6)
>4 ≤6 mm	2.4% (n = 8)	5.2% (n = 5)	8.0% (n = 6)	19.0% (n = 11)
>6 ≤10 mm	2.1% (n = 7)	1.0% (n = 1)	6.7% (n = 5)	5.1% (n = 3)
>10 mm	–	1.0% (n = 1)	1.3% (n = 1)	6.8% (n = 4)
No follow-up	23.6% (n = 78)	20.6% (n = 20)	18.7% (n = 14)	17.2% (n = 10)
Patient no-show	1.8% (n = 6)	2.1% (n = 2)	2.7 % (n = 2)	1.7% (n = 1)
No longer in Scania	0.3% (n = 1)	–	–	–

SFR – stone-free rate

Table 3b. *Preoperative stone size and stone-free rate*

Preoperative stone size	≤2 mm (n = 10)	>2≤4 mm (n = 102)	>4≤6 mm (n = 183)	>6≤10 mm (n = 228)	>10 mm (n = 44)
SFR	100% (n = 10)	100% (n = 102)	96.2% (n = 176)	84.6% (n = 193)	68.2% (n = 30)

SFR – stone-free rate

Age, sex, Charlson Comorbidity Index score, diabetic comorbidity, long-term mortality, and the Clavien-Dindo classification score are presented in Table 1. The overall SFR was 90.7% (515/56799 (Table 2). All patients who were readmitted within 14 days (Figure 1) scored ≥1 according to Clavien-Dindo system [15]. Data regarding stone location in the ureter, stone size, and the use of ureteral stents are presented in Table 2. SFR's determined by preoperative stone location are presented in Table 3a.

Table 3c. *Size of residual stones needed to be re-treated within 6 months*

	Re-treated patients within 6 months (n = 20)
Size of residual stone	
≤2 mm	10.0% (n = 2)
>2 ≤4 mm	10.0% (n = 2)
>4 ≤6 mm	30.0% (n = 6)
>6 ≤10 mm	35.0% (n = 7)
>10 mm	15.0% (n = 3)

SFR provided preoperative stone size showed 100 % success rate in stones ≤4 mm (n = 112). SFR for stones >4≤6 mm 96.2 % (176/183), for stones >6≤10 mm 84.6 % (193/228), and for >10 mm 68.2 % (30/44) (Table 3a and 3b).

Of the 20 patients re-treated for the same stone within 6 months, 4 patients (20.0%) had a residual stone size of ≤4 mm (Table 3c). This equaled 10.5 % (4/38) out of all patients with residual stones, considered stone-free.

Operating with the on-call OR (operating room) nursing staff or the evening or night staff, we found a SFR of 97.6% (1/41) compared to the SFR of 89% (52/474) during normal working hours; when compensating for age/gender we found no significant difference.

A positive urine culture was found in 15.9% of the patients (90/567). The most common pathogen was Escherichia coli (32/90, 35.6%) and the second most common was Enterococcus faecalis (17/90, 18.9%). A total of 79 patients (13.9%) received preoperative antibiotic treatment, 341 patients (60.1%) received perioperative antibiotics, and 103 patients (18.2 %) received postoperative antibiotics treatment. Of the perioperative antibiotics, aminoglycoside was the most used type (235/341, 69.0%) (Table 4).

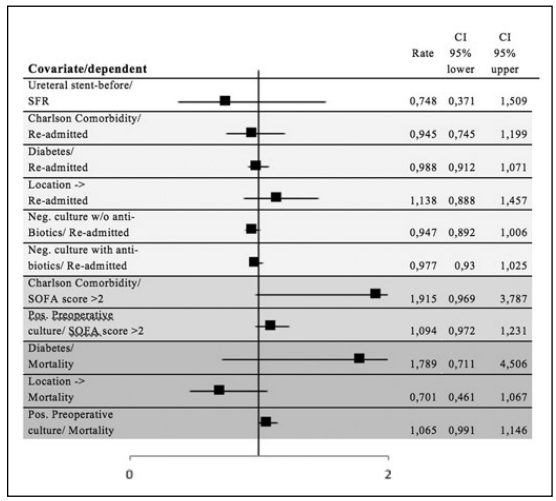


Figure 2. *Forest plot of univariate logistic regression analyses without significant P-value.*

Data regarding patients seeking medical attention within 14 days are presented in Table 5. 60 patients (10.6%) sought medical attention within 14 days, of these 40 (7.1%) were readmitted. The causes of re-admission were infection (19/60, 31.7%), pain (13/60, 21.7%), bleeding (6/60, 10.0%), and other causes (2/60, 3.3%).

Table 4. *Preoperative urine culture and antibiotics treatment*

	All patients (n = 567)	Patients not seeking medical care within 14 days (n = 507)	Patients seeking medical care within 14 days (n = 60)
Positive urine culture	15.9% (n = 90)	14.0% (n = 71)	31.7% (n = 19)
E. Coli	35.6% (n = 32/90)	39.4% (n = 28/71)	21.1% (n = 4/19)
Enterococcus faecalis	18.9% (n = 17/90)	21.1% (n = 15/71)	10.5% (n = 2/19)
Other bacteria	45.5% (n = 41/90)	39.4% (n = 28/71)	68.4% (n = 13/19)
Preoperative antibiotics	13.9% (n = 79)	13.2% (n = 67)	20.0% (n = 12)
Ciprofloxacin	25.3% (n = 20/79)	28.4% (n = 19/67)	8.3% (n = 1/12)
TMP/SMX	19.0% (n = 15/79)	19.4% (n = 13/67)	16.7% (n = 2/12)
Other antibiotics	55.7% (n = 44/79)	52.2% (n = 35/67)	75.0% (n = 9/12)
Perioperative antibiotics	60.1% (n = 341)	59.4% (n = 301)	66.7% (n = 40)
Aminoglycoside	69.0% (n = 235/341)	67.4% (n = 203/301)	80.0% (n = 32/40)
Other antibiotics	31.0% (n = 106/341)	32.6% (n = 98/301)	20.0% (n = 8/40)
Postoperative antibiotics	18.2% (n = 103)	17.8% (n = 90)	21.7% (n = 13)
Ciprofloxacin	36.9% (n = 38/103)	38.9% (n = 35/90)	23.1% (n = 3/13)
TMP/SMX	34.0% (n = 35/103)	34.4% (n = 31/90)	30.8% (n = 4/13)
Other antibiotics	29.1% (n = 30/103)	26.7% (n = 24/90)	46.1% (n = 6/13)
Days of antibiotic treatment, Mean (range)	2.3 (0–30)	2.2 (0–30)	2.8 (0–25)

TMP/SMX – trimethoprim/sulfamethoxazole; E. Coli – Escherichia coli

Of the patients admitted, 12 (20.0%) had a SOFA (Sequential sepsis-related organ failure assessment) score ≥2 and one patient was admitted to the ICU [16]. Logistic regression model with SFR, re-admission, SOFA score >2, or mortality as a dependent factor, without statistical significance, are presented in Figure 2 as a forest plot. The univariate logistic regression analyses showing statistical significance are presented in Table 6. Parameters obtaining $p \leq 0.05$ were further investigated in multivariate logistical regression, adding the predefined confounding variables of gender and age. SFR is significantly

Table 5. *Characteristics of patients with complications*

	Patients seeking medical care within 14 days (n = 60)	Patients seeking medical care within 14 days, but not re-admitted (n = 20)	Patients seeking medical care within 14 days, re-admitted (n = 40)
Age, Mean (±SD)	56.7 (18.1)	59.4 (17.6)	55.4 (18.3)
Sex M:F Ratio	2:1	4:1	1.5:1
Cause of admission			
Infection	33.3% (n = 20)	5.0% (n = 1)	47.5% (n = 19)
Bleeding	13.3% (n = 8)	10.0% (n = 2)	15.0% (n = 6)
Pain	40.0% (n = 24)	55.0% (n = 11)	32.5% (n = 13)
Other	13.3% (n = 8)	30.0% (n = 6)	5.0% (n = 2)
Days until re-admission, Mean (range)	4.3 (0–14)	3.6 (0–14)	4.8 (0–14)
Days of re-hospitalisation, Mean (range)	3.1 (0–20)	–	4.6 (1–20)
Blood culture drawn	40.0% (n = 24)	–	60.0% (n = 24)
Urine culture drawn	63.3% (n = 38)	40.0% (n = 8)	75.0% (n = 30)
Positive culture	21.7% (n = 13)	10.0% (n = 2)	27.5% (n = 11)
Escherichia coli	38.5% (n = 5/13)	100% (n = 2/2)	27.3% (n = 3/11)
Enterococcus faecalis	7.7 % (n = 1/13)	–	9.1% (n = 1/11)
Other bacteria	53.8% (n = 7/13)	–	63.6% (n = 7/11)
Antibiotics	60.0% (n = 36)	30.0% (n = 6)	75.0% (n = 30)
Ciprofloxacin	38.9% (n = 14/36)	33.3% (n = 2/6)	40.0% (n = 12/30)
TMP/SMX	13.9% (n = 5/26)	16.7% (n = 1/6)	13.3% (n = 4/30)
Aminoglycoside	30.6% (n = 11/36)	33.3% (n = 2/6)	30.0% (n = 9/30)
Otherantibiotics	16.7% (n = 6/36)	16.7% (n = 1/6)	16.7% (n = 5/30)
ICU	1.7% (n = 1)	–	2.5% (n = 1)
SOFA score ≥2	20% (n = 12)	5.0% (n = 1)	27.5% (n = 11)

TMP/SMX – trimethoprim/sulfamethoxazole

Table 6. *Univariate logistical regression analyses showing statistical significance*

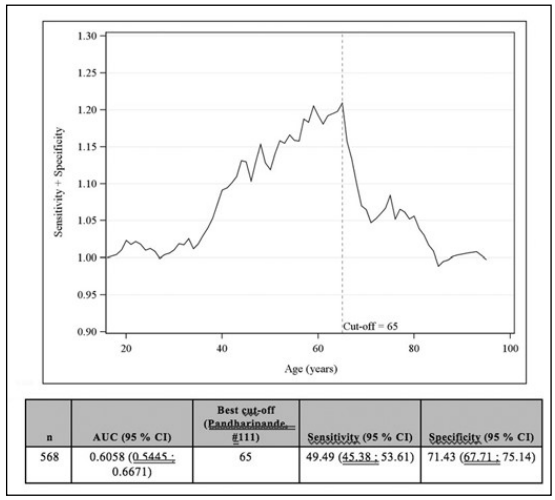
	P-value	OR	CI 95%
On call personal to SFR	0.141	0.222	0.606–33.378
Not normal working hours to SFR	0.141	0.222	0.606–33.378
Stone location in ureter to SFR	<0.001	0.482	0.376–0.616
Preoperative stone size to SFR	<0.001	0.885	0.852–0.920
Postoperative ureteral stent to SFR	0.002	0.413	0.237–0.721
Clavien-Dindo to re-admission	<0.001	7.996	5.318–12.022
Positive preoperative urine culture to readmission	0.001	1.100	1.041–1.161
Clavien-Dindo to mortality	0.022	1.557	1.065–2.278
Charlson Comorbidity index to mortality	<0.001	1.869	1.506–2.320
SOFA score ≥2 to mortality	0.023	15.667	1.460–168.074
Clavien-Dindo to SOFA score ≥2	0.003	5.426	1.788–16.466
Age to SOFA score ≥2	0.014	1.062	1.012–1.115

SFR – stone-free rate; SOFA – sequential sepsis-related organ failure assessment

affected by stone location in the ureter (p <0.001, OR 0.515, CI 95% 0.389–0.682), preoperative stone size (p <0.001, OR 0.728, CI 95% 0.654–0.810), and postoperative ureteral stents (p = 0.009, OR 0.418, CI 95% 0.217–0.804). Using readmission as a dependent, only the Clavien-Dindo classification (p <0.001, OR 8.014, CI 95% 5.220–12.304) was confirmed to be significant. Mortality was not increased if the patient was readmitted within 14 days.

The risk of surgical complications in regard to the time of day (0800–1700 vs. other), ordinary vs. on call personal, acute vs elective surgery and flexible vs semi-rigid ureteroscope, no significant differences were found (Table 7). Age, however, was significant in all groups and the receiver operating characteristic (ROC) curve analysis was performed [16]. Most accurate cut-off point of age, regarding age and the risk of complications, was 65 years (area under curve (AUC) 0.6) (Figure 3).

Charlson Comorbidity index, preoperative stone size, and stone location in the ureter to Clavien-Dindo showed no statistical significant association with postoperative risk for complications (p = 0.227, p = 0.274, p = 0.720, respectively) (Figure 2). A univariate logistical regression analysis was made with diabetes [17] to Clavien-Dindo (dependent) showing no statistical significance (p = 0.717).



n	AUC (95 % CI)	Best cut-off (Pandharipande, 2011)	Sensitivity (95 % CI)	Specificity (95 % CI)
568	0.6058 (0.5445 ; 0.6671)	65	49.49 (45.38 ; 53.61)	71.43 (67.71 ; 75.14)

Figure 3. *Recevier operating characteristic (ROC) curve describing sensitivity + specificity vs. age for risk of complications and ROC curve.*

DISCUSSION

Regarding the definition of surgical success, there are different ways to report this; however, the older SFR meaning 'Stone Free Rate' used when the residual fragments are <4 mm and hence corresponds well to the newer 'Successful treatment' having the same definition. The SFR of 90.1% found in this study is comparable to similar studies [6]. Georgescu et al. showed similar results (SFR 90.9%) [18]. Somani et al. reported a SFR of 85.6% in a multi-center worldwide cohort [19]. Ghani & Wolf [20] reviewed multiple studies in order to determine a SFR for URS. Stone-free (no residual stones) was found in 51%, with a cut- off of ≤2 mm, a SFR of 77% was found, and with a cut-off of ≤4 mm a total SFR of 84.5% was found. Compared to our data (<2 mm/86.9% and <4 mm/83.4%, respectively), the success rate seems to be slightly higher at our center. In a worldwide study includ-

Table 7. *Logistical regression analyses regarding hour of surgery, normal vs. call-time surgery, acute vs. elective surgery and flexible vs. semi-rigid ureteroscope and the risk of complications*

Model	Variable	OR (95% CI)	p-value
Time of day	08.00–17.00 vs. other time of day	0.5754 (0.2186; 1.5145)	0.2630
	Age	1.0230 (1.0085; 1.0377)	0.0018
	Men vs. women	1.0781 (0.6562; 1.7713)	0.7664
Night / Call	Night / Call vs. daytime	0.5380 (0.2583; 1.1204)	0.0977
	Age	1.0224 (1.0080; 1.0371)	0.0023
	Men vs. women	1.0870 (0.6612; 1.7868)	0.7423
Acute	Acute vs. elective	0.7539 (0.4400; 1.2919)	0.3040
	Age	1.0218 (1.0073; 1.0365)	0.0032
	Men vs. women	1.0700 (0.6510; 1.7588)	0.7895
Flexible	Flexible vs. standard	1.6526 (0.9386; 2.9095)	0.0818
	Age	1.0224 (1.0078; 1.0371)	0.0025
	Men vs. women	1.1227 (0.6815; 1.8494)	0.6496

ing 9681 patients operated with URS, SFR in different parts of the ureter was: 94.2% in the distal third part of the ureter, 89.4% in the middle third part of the ureter, and 84.5% in the proximal third part of the ureter [6]. This is equivalent to our results. As expected, our statistical analysis could confirm that the more distal the stone was, the more probable was a successful stone removal ($p < 0.001$).

The term "clinically insignificant residual stones" remains debated [21]. In an early, prospective study following 160 patients with remaining stone fragments of ≤4 mm after receiving ESWL treatment, about 40% had symptomatic episodes and required intervention [22]. Rebuck et al. [23] evaluated the natural course of post-URS remaining fragments, using a CT-scan to follow fragments ≤4 mm, and showed that 13% of patients with residual fragments ≤4 mm needed to be re-treated. In our study, 10.5% (4/38) of patients with residual fragments ≤4 mm underwent re-URS within 6 months. Treating residual stones ≤4 mm is debatable. There is a significant chance of spontaneously passage, 79.6% passes within 20 weeks according to Jendeberg et al. [24] . If this corresponds to residuals after surgery in the not known. Their data showed the rate of spontaneous passage were 98% in stones >3 mm, 81% in stones 4 mm, 65% in stones 5 mm, 33% in stones 6 mm, and 9% in stones ≥6.5 mm. Our data could show that a significantly higher SFR was reached among smaller stones ($p < 0.001$).

Preoperative ureteral stenting may affect the success rate of the URS. A meta-analysis of nine retrospective studies with a total of 11,239 patients showed a higher SFR if the patient had received a preoperative ureteral stent [25], confirmed in other studies [26]. If the positive effect on SFR by preoperative stenting is due to stone location / stone burden or by stenting itself, remains unclear [9]. Our data show no significant effect of preoperative stenting on SFR ($p = 0.417$) which also Nabi et al. [10] found. Regarding postoperative stenting we found a negative correlation to SFR ($p = 0.002$) (independent of age, gender, stone size, and stone location). This might be explained by local clinical practice, stents were used for the most complicated cases having longer operating time.

Correlation between the positive urine culture prior to URS to positive urine culture at readmission showed no significance ($p = 0.211$). All patients with positive urine culture prior to the treatment received antibiotics pre-, peri-, and/or postoperatively. Our data showed a tendency ($p = 0.070$) that patients with negative urine culture prior to URS not receiving antibiotics had a higher incidence of positive urine culture at readmission maybe indicating infection as a result of surgery or the effect of bacteria in/on the stone. As expected, a third of the urine cultures show growth of Escherichia coli (35.6%). The increasing resistance in Escherichia coli to antibiotics is alarming [27]. Our study shows a use of ciprofloxacin in approximately 30% of patients, and TMP/SMX in almost 25%. Regardless of its accordance with the EAU - Guidelines on Urolithiasis at the time, this might contribute to increasing resistance in the future.

It is noteworthy that of patients being re-admitted, 11 had positive urine and/or blood culture, and all SOFA score ≥2. URS treatment itself may entail a risk of impacting creatinine levels [28], maybe giving all our patients a SOFA score of 1. Study limitations with retrospective data, trying to classify the qSOFA/SOFA score requires lots of work and patients rarely are classified according to this algorithm which could lead to inaccuracy.

Perez et al. [6] showed an intraoperative complication rate of 3.8–7.7%, and a postoperatively complication rate of 2.4–4.6% depending on stone location, including bleeding, infection, pain, and others. This can be compared to a complication rate of around 6% in ESWL, and approximately 10% in PCNL [8]. Our data show a re-admission rate/complication rate of 7.1/10.7%.

We show no increased risk for postoperative complications in patients with comorbidities classified with the Charlson Comorbidity index ($p = 0.720$), nor in patients with diabetes ($p = 0.717$). According to our findings there were no correlation between an increased risk of complications and stone location ($p = 0.227$) or stone size (0.274). This study does not show an increased risk for complications when surgery is performed with on-call personal or if it is performed acute and the time (day/night) does not seem to matter. The possibility of selection bias regarding this group and a tendency to only do uncomplicated stones outside normal working hours could be one explanation. Another could be that on-call surgery was performed only by senior consultants. Since the numbers are small, larger studies are needed. Studies have indicated that the risk of complications does not increase with age [29]. In our study the risk of complications seems to increase with age and the ROC curve analysis indicates that a possible cut off at 65 years might be recommended.

As in other retrospective cohort studies, we have had to rely on the documenting doctor/nurse for all retrospective data. Some of our findings are based on small numbers and errors in documentation might lead to shifts in our data analyses.

CONCLUSIONS

According to our findings performing ureteroscopy outside 'office hours' does not increase the complica-

tion rate. Outcome of URS treatment in the northwestern part of Scania County, Sweden, seems to be in parity with previous studies.

We conclude that there are a few complications to modern URS treatment and that stone-free rate (SFR) is high. URS seems to be a safe and effective method for treating ureteral stones regardless of location, but should preferably be used for stones in the lower part of the ureter. In this study, we found no significant risk factors for complications. E. coli is the most common bacteria in preoperative cultures. The risk of complications increases with age and for patients older than 65 years another modality than URS could be considered.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This work was supported by Gorthon foundation, Lions foundation, Percy Falk foundation and ALF Region Skåne.

ACKNOWLEDGMENTS

We like to thank the staff at the Department of Urology, Helsingborg and Ängelholms hospital for helping with patient registration.

Appendix 1

Updated Charlson Comorbidity Index (Quan, 2011 #71). Used to predict long-term mortality among patients with chronic disease(s). The updated score of the Index was used, validated to modern treatment of these disease(s).

Variable	Updated Charlson Score
Charlson comorbidity	
Myocardial infarction	0
Congestive heart failure	2
Peripheral vascular disease	0
Cerebrovascular disease	0
Dementia	2
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	0
Mild liver disease	2
Diabetes without chronic complications	0
Diabetes with chronic complications	1
Hemiplegia or paraplegia	2
Renal disease	1
Any malignancy, including leukaemia /lymphoma	2
Moderate or severe liver disease	4
Metastatic solid tumour	6
AIDS/HIV	4
Maximum comorbidity score	24

AIDS – acquired immunodeficiency syndrome; HIV – human immunodeficiency virus

The following comorbid conditions were mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild liver disease and moderate or severe liver disease; and any malignancy and metastatic solid tumour.

Appendix 2

The Clavien-Dindo Classification, used to classify surgical complications [40].

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management.
Grade V	Death of a patient.

References

1. Lyu J, Wu R. A brief history of recognition on urolithiasis before medieval period. Zhonghua Yi Shi Za Zhi. 2014; 44: 36-39.
2. Ljunghall S. Incidence and natural history of renal stone disease and its relationship to calcium metabolism. Eur Urol. 1978; 4: 424-430.
3. Ahlstrand C, Tiselius HG. Recurrences during a 10-year follow-up after first renal stone episode. Urol Res. 1990; 18: 397-399.
4. Trinchieri A. Epidemiology of urolithiasis: an update. Clin Cases Miner Bone Metab. 2008; 5: 101-106.
5. Hesse A, Brandle E, Wilbert D, Köhrmann KU, Alken P. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. Eur Urol. 2003; 44: 709-713.
6. Perez Castro E, Osther PJ, Jinga V, et al. Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: the Clinical Research Office of the Endourological Society ureteroscopy global study. Eur Urol. 2014; 66: 102-109.
7. Drake T, Grivas N, Dabestani S, et al. What are the Benefits and Harms of Ureteroscopy Compared with Shock-wave Lithotripsy in the Treatment of Upper Ureteral Stones? A Systematic Review. Eur Urol. 2017; 72: 772-786.
8. Turk C, Petrik A, Sarica K, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016; 69: 475-482.
9. Rubenstein RA, Zhao LC, Loeb S, Shore DM, Nadler RB. Prestenting improves ureteroscopic stone-free rates. J Endourol. 2007; 21: 1277-1280.
10. Nabi G, Cook J, N'Dow J, McClinton S. Outcomes of stenting after uncomplicated ureteroscopy: systematic review and meta-analysis. BMJ. 2007; 334: 572.
11. Lingeman JE, Newman D, Mertz JH, et al. Extracorporeal shock wave lithotripsy: the Methodist Hospital of Indiana experience. J Urol. 1986; 135: 1134-1137.
12. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014; 28: 1-13.
13. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. Eur Urol. 2007; 52: 1610-1631.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-383.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240: 205-213.
16. Rosenschein U, Budde-Schwartzman B. Ultrasound coronary angioplasty: state of the art and new clinical aspects. Herz. 1997; 22: 308-317.
17. Bai J, Lin J, Zhuang H, Guo D, Yang X, Duan M. Changes in plasma cholesterol level and risk factors of death in patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2016; 28: 164-168.
18. Georgescu D, Multescu R, Geavlete B, Geavlete P. Intraoperative complications after 8150 semirigid ureteroscopies for ureteral lithiasis: risk analysis and management. Chirurgia (Bucur). 2014; 109: 369-374.
19. Somani BK, Giusti G, Sun Y, et al. Complications associated with ureterorenoscopy (URS) related to treatment of urolithiasis: the Clinical Research Office of Endourological Society URS Global study. World J Urol. 2017; 35: 675-681.
20. Ghani KR, Wolf JS, Jr. What is the stone-free rate following flexible ureteroscopy for kidney stones? Nat Rev Urol. 2015; 12: 363.
21. Deters LA, Jumper CM, Steinberg PL, Pais VM Jr. Evaluating the definition of 'stone free status' in contemporary urologic literature. Clin Nephrol. 2011; 76: 354-357.
22. Streem SB, Yost A, Mascha E. Clinical implications of clinically insignificant store fragments after extracorporeal shock wave lithotripsy. J Urol. 1996; 155: 1186-1190.
23. Rebuck DA, Macejko A, Bhalani V, Ramos P, Nadler RB. The natural history of renal stone fragments following ureteroscopy. Urology. 2011; 77: 564-568.
24. Jendeberg J, Geijer H, Alshamari M, Cierzniak B, Lidén M. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. Eur Radiol. 2017; 27: 4775-4785.

25. Yang Y, Tang Y, Bai Y, Wang X, Feng D, Han P. Preoperative double-J stent placement can improve the stone-free rate for patients undergoing ureteroscopic lithotripsy: a systematic review and meta-analysis. Urolithiasis. 2018; 46: 493-499.

26. Assimos D, Crisci A, Culkin D, et al. Preoperative JJ stent placement in ureteric and renal stone treatment: results from the Clinical Research Office of Endourological Society (CROES) ureteroscopy (URS) Global Study. BJU Int. 2016; 117: 648-654.

27. Folkhälsomyndigheten. Escherichia coli. Resistensläge [Internet] 2017 [cited 2017 2017-12-05]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/sjukdomsstatistik/escherichia-coli/?t=county

28. Benli E, Ayyildiz SN, Cirrik S, Noyan T, Ayyildiz A, Cirakoglu A. Early term effect of ureterorenoscopy (URS) on the Kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine. Int Braz J Urol. 2017; 43: 887-895.

29. Daels FP, Gaizauskas A, Rioja J, et al. Age-related prevalence of diabetes mellitus, cardiovascular disease and anticoagulation therapy use in a urolithiasis population and their effect on outcomes: the Clinical Research Office of the Endourological Society Ureteroscopy Global Study. World J Urol. 2015; 33: 859-864.

Paper III

SCANDINAVIAN JOURNAL OF UROLOGY
https://doi.org/10.1080/21681805.2020.1740316

ARTICLE

Percutaneous nephrolithotomy and modern aspects of complications and antibiotic treatment

Magnus Wagenius[a,b], Jasmine Borglin[b], Marcin Popiolek[c], Andreas Forsvall[b], Johan Stranne[d] and Adam Linder[a]

[a]Department of Clinical Sciences, Division of Infection Medicine, Lund University, Lund, Sweden; [b]Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden; [c]Department of Urology, Örebro University Hospital, Örebro, Sweden; [d]Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT

Objective: The incidence of urinary stones is increasing across the globe. Surgical treatment includes extracorporal shock-wave lithotripsy (ESWL), ureterolithotripsy (URS), percutaneous nephrolitotomy (PCNL) and rarely open surgery. This single center study describes complications to PCNL focusing on infections, bacterial growth/resistance and antibiotic prophylaxis/treatment.

Materials and methods: All patients treated for kidney stones with PCNL at Ängelholm Hospital in north-western Scania, Sweden from January 2009 to December 2015 were included. A dipstick test and a bacterial culture was made on all patients. Kidney stones were analysed for composition and cultured for bacteria.

Results: In total, 186 patients underwent PCNL, all receiving perioperative antibiotics. Thirty percent (56/186) had a positive urinary culture taken before surgery and 33.3% (62/186) had positive stone culture. The concordance between urinary and stone culture was 57.1%. Both positive stone and urinary culture increased the risk of complications after surgery ($p = 0.002$ and $p = 0.017$, respectively). Complications occurred in 16% (30/186). Eight patients (4.3%) developed sepsis. The most common bacteria in urine were *Enterococcus faecalis* and *Escherichia coli*, both 20%. The most common stone-bacteria reported was *Enterococcus faecalis* (26%).

Conclusion: This study has a total complication rate of 16%, approximately 10% of those are severe. The most common complication to PCNL was infection (60%), followed by bleeding (5.4%), reoperation (1.6%) and pain (0.5%). The high prevalence of *E. faecalis* might need to be considered, however the results should be validated in a larger cohort, possibly with a higher rate of antibiotic resistance, before a change of guidelines regarding prophylactic antibiotics could be proposed.

ARTICLE HISTORY
Received 17 October 2019
Revised 28 January 2020
Accepted 4 March 2020

KEYWORDS
Ureteroscopy; infection; complications; ureteric stone

Introduction

Kidney stones are common globally. The prevalence and incidence rates are 1.7–14.8% and 114–720/100,000 individuals, respectively. Epidemiologic data from seven Western countries show that incidence and prevalence are increasing [1]. In Sweden, the prevalence of nephrolithiasis was 10% for males and 3% for females in the 1970s [2], now gender differences are starting to equalize [3].

Kidney stones are composed of minerals, often containing organic components. Supersaturation of a mineral in the urine leads to stone formation. Calcium oxalate/calcium phosphate stones are the most common (80%), other components are struvite, uric acid and cysteine [4]. Struvite stones or 'infection stones' form in the presence of urease producing bacteria, sometimes growing quickly to large stones, 'staghorn calculi' [5].

Nephrolithiasis is multifactorial and can be caused by several different underlying diseases and numerous genetic (hypercalciuria, gout and cystinuria) [6] and environmental factors [7]. Weight, body mass index [8] and diabetes mellitus [9] also increase the incidence of kidney stones, sometimes as parts in the metabolic syndrome. Dietary risk factors are sodium and animal protein intake. The single most important factor to reduce stone formation is hydration.

Stones are formed in the kidneys and can move to the ureter, leading to obstruction and causing renal colic. Ureteric stones up to 7 mm most often pass spontaneously. The majority of stones greater than 7 mm require urological intervention [10]. Open renal stone surgery is now rarely performed, since the development of extracorporeal shock wave lithotripsy (ESWL), flexible ureteroscopy and percutaneous nephrolithotomy (PCNL) [11].

PCNL, first described by Fernström and Johansson in 1976 [12], is today the modality of choice for patients with kidney stones greater than 1.5–2 cm, lower pole stones greater than 1–1.5 cm, staghorn stones and shock-wave resistant stones [10].

Known complications to PCNL are fever (2.8–32.1%), bleeding requiring transfusion (0–45%), organ injury (0–1.7%) and sepsis (0.3–5%) [13]. The EAU Guidelines recommend

CONTACT Magnus Wagenius magnus.wagenius@gmail.com Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden.

urinary culture and treatment of all urinary infections preoperatively [10]. Positive stone culture and pelvic urine culture seem to be better predictors of urosepsis than midstream bladder urine [14].

This study evaluates the treatment and complication outcomes of PCNL performed during 2009–2015 at a single centre in Sweden. The aim was to identify risk factors causing complications focusing on postoperative infectious complications.

Materials and methods

This is a single-centre observational study. We included all patients operated on with PCNL at the Urology Clinic in north-western Scania County (Ängelholm Hospital) between the years 2009–2015 ($n = 186$). The main part of the data were prospectively gathered according to protocol, Clavian and the more complex situation of all antibiotic treatment was retrospectively gathered from medical charts. All operations were on Mondays or Tuesdays and the culture was taken for 1 week (this differs, however, sometimes due to the patients). The aim was that the patient should receive adequate antibiotic and start at least 3 days before surgery.

The primary outcome of the study was the incidence of sepsis and febrile urinary tract infections. Secondary outcomes were other complications (e.g. bleeding, complications requiring re-surgery/intervention, bacterial growth, stone composition, antibiotic prophylaxis/treatment and residual stones). Data collected was: Age at intervention, sex, body mass index, preoperative urine culture including resistance pattern, stone culture, pre-, per- and postoperative antibiotics, stone composition, stone cultures, stone free rate (SFR), sepsis and bleeding complication, days of hospitalization following surgery, comorbidity, catheter use and mortality rate (Figure 1). Exposure variables: positive urinary and/or stone culture, antibiotic prophylaxis. We considered patients with residual stones < 4 mm as stone free and used this as a cut-off when calculating SFR. The diagnosis of sepsis was determined by the treating physician and re-evaluated with qSOFA according to the SEPSIS-3 consensus definitions [15]. Complications were registered and categorized according to CROES modified Clavien-Dindo [16,17] (Appendix 1). Complications requiring medical care were divided into subgroups; acute ($<$ 30 days) and late onset ($>$ 30 days). Treatment indications were kidney stones $>$ 1.5 cm, infectious stones, continual discomfort such as pain or bleeding/infection due to the stone, ESWL-resistant stones and anatomic anomalies preventing stone passage through the urinary tract. All patients had a dipstick and a urinary culture taken preoperatively. A new culture was taken if the patients developed infections symptoms. Targeted antibiotic therapy according to culture results and resistance pattern was administered prior to surgery. In cases of negative dipstick or culture, patients received standard antibiotic perioperative (Cefotaxime 1 g $\times$ 2 intravenously). Intravenous antibiotic therapy was started on the morning of the day of surgery and continued until the removal of the nephrostomy tube, normally on day 2 after surgery. Regarding additional antibiotic treatment this was decided by the treating surgeon and related to infectious symptoms considering the cultures taken. All patients underwent a CT scan preoperatively to assess the anatomy and location of the stone. The surgical procedure was initiated by cystoscopy and placement of a ureteral catheter (open-end, 7 Ch.) on the treating side (normally guided by a Terumo® stiff guide wire with floppy end, 0.035"). A regular catheter (14 Ch.) was placed and the patient turned to prone position. With guidance of contrast and fluoroscopy, a dorsal normally caudal renal calyceal papilla was punctured, 9–30 Ch. dilatations were done before placing an Amplatz™ sheath. The stones were fragmented by ultrasound (EMS Swiss Lithoclast®) and a nephrostomy 18 Ch. with open end was left in place, to be removed usually 2 days after surgery.

Long-term mortality was evaluated through the Swedish population registry, on 7 May 2018. The follow-up time varied between 2 and 9 years. No mortality was registered within 3 months following PCNL. Chi-square and Fisher's exact test were used for statistical calculations where appropriate. Regarding cultures the laboratory diagnosis is based on colony counts following culture, which reflect the concentration of bacteria in urine and, hence, the likelihood that the bacteria grown arise from a UTI rather than contamination. UTI is normally caused by a single bacteria present in a high concentration, usually $\geq$ 10*8 CFU/L.

All urine samples were transported in refrigerated boxes to a central microbiology laboratory, Lund University Hospital, Lund, Sweden, and cultured on selective media (10 µL on CNA agar, 10 µL on Uricult chromogenic agar) (Figure 2).

Growth was identified to species level and susceptibility tested according to the standard methods used at the laboratory at the time of culture. Bacterial growth was semi-quantified as scarce ($<$ 10*7 CFU/L), intermediate (10*7 – 10*8 CFU/L) or rich ($>$ 10*8 CFU/L). Workup was performed if there was growth of 1–2 primary or secondary pathogens. Growth of three or more species was just reported as 'mixed flora'.

Urinary stones were placed in standard urine collection tubes and transported in refrigerated boxes to the same laboratory. Upon arrival at the laboratory they were transferred to Trypticase Soy Broth, crushed and/or sonicated for 2 min, vortexed and 3 droplets each were cultured on blood-, hematin- and Uricult chromogenic agars. All growth was identified to species level and susceptibility tested without quantification.

Stone analysis were performed at Sahlgrenska University Hospital using ATR FT-IR.

This study was approved by the regional ethics review committee in Lund (Dnr 2017/15).

Results

All 186 patients undergoing PCNL during 2009–2015 at Ängelholm Hospital are presented in Tables 1 and 2. Of the patients, 1.6% (3/186) had a urethral catheter, 14.5% (27/186) had a double JJ-catheter and 11.8% (22/186) had a

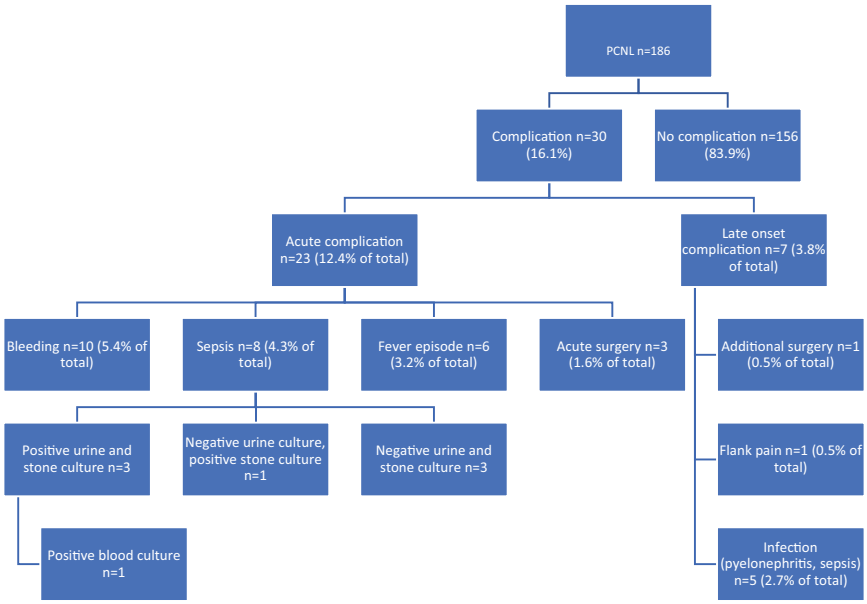


Figure 1. Flow chart of patients and complications. Acute complication = complication prior to discharge. Late onset complication = complications after discharge, but within 30 days. Additional surgery does not include surgery with the sole purpose of removing residual stones.

nephrostomy catheter preoperatively. Of all, 30.1% (56/186) had a positive urine culture preoperatively (Tables 3 and 4). The most common bacteria were *Enterococcus faecalis* (*E. faecalis*) and *Escherichia coli* (*E. coli*), with 19.6% (11/56) in both cases, followed by *Streptococcus agalactiae*, 12.5% (7/56). Mixed flora was common, 23.2% (13/56) (Figure 3(a)). One culture was positive for *E. coli* with carbapenemase production (carbapenem-hydrolyzing oxacillinase-48 (OXA-48)).

Stone culture were positive ($> 10^3$ colony forming units/ml) in 33.3% (62/186) (Table 3). The most common bacteria reported were *E. faecalis*, 25.8% (16/62) followed by coagulase-negative staphylococci, 24.2% (15/62) and *E. coli*, 16.1% (10/62) (Figure 3(a)). Both positive urine and stone culture were found in 18.8% (35/186). The concordance rate between urine and stone cultures was 57.1% (20/35), and 60% of these (12/20) also displayed the same resistance pattern. A positive urine culture increased the risk of complications. Microbial pathogens growing in cultures from stone or urine are shown in Table 5.

Of the 186 stones, only 176 were available for analysis. In complex stones the combination of calcium, oxalate and phosphate was the most common, occurring in 58.5% (103/176). Calcium were detected in 92.0% (162/176), oxalate in 79.5% (140/176) and phosphate in 69.9% (123/176) of the stones. Other components analyzed were ammonium, urate, magnesium, uric acid, struvite, carbon dioxide and trioxide and cysteine (Figure 4).

All patients received antibiotic prophylaxis (Table 3). The most common intravenous antibiotic was Cefotaxime, 78% (145/186), followed by aminoglycosides, 24.2% (45/186). Most patients received intravenous antibiotics preoperatively alone (83.3% (155/186)). Patients with a positive culture received oral antibiotics followed by intravenous antibiotics (13.4% (25/186)). Additional postoperative antibiotics, after removal of the nephrostomy tube, were given to 48.9% (91/186) of the patients. Of these, Ciprofloxacin (500 mg × 2 for 7 days), 47.3% (43/91) and Pivmecillinam (200 mg × 3 for 7 days) ,25.3% (23/91) were the most commonly used antimicrobial agents (Table 3).

Out of the patients with a positive urine culture, 44.6% (25/56) received oral antibiotics tailored to culture results and resistance pattern prior to admission and the rest of the positive cultures were considered bacterial contamination. The patients receiving antibiotics prior to admission had a higher risk of developing any complications ($p = 0.008$), but not sepsis ($p = 0.315$) compared to those who did not receive per oral antibiotics.

A total complication rate of 16.1% (30/186), 23 during hospital stay and seven occurring within 30 days, was found in this study. Positive urinary culture or stone culture was associated to the development of any complication, $p = 0.017$ and $p = 0.002$, respectively (Table 5).

Stone free rate was 65.6% (122/186). Treatment of residual stones were: watchful waiting, $n = 40$, ESWL, $n = 15$, ureteroscopy, $n = 8$, and endoluminal antegrade approach, $n = 1$.

No other possible risk-factors show any significant correlation with complications (age, sex, body mass index, stone composition, stone free rate (SFR), comorbidity, catheter use and mortality rate).

No significant association was found between serious postoperative infectious complications defined as sepsis and

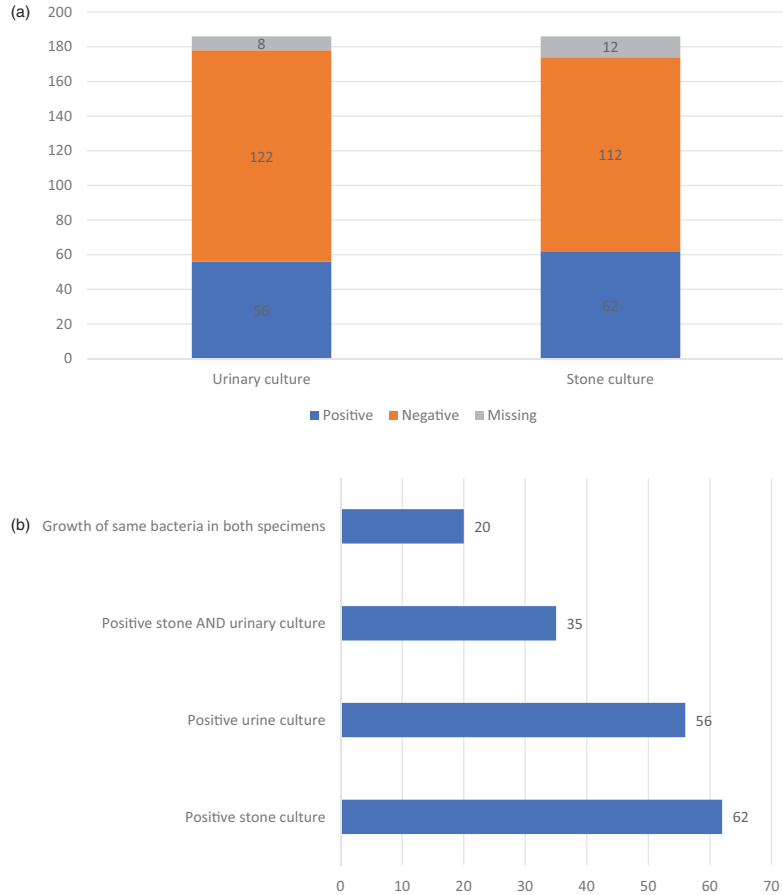


Figure 2. (a) Overview of urinary and stone culture ($n = 186$). (b) Overview of culture and concordance in the 186 patients.

Table 1. Patient demographics and complications.

		All patients ($n = 186$)	No complication ($n = 156$)	Complications ($n = 30$)
Age, mean (95% CI)		59.6 (57.3–61.9)	59.2 (56.7–61.6)	61.8 (55.5–68.1)
Sex male, % (*n*)		55.9% (104)	57.1% (89)	50.0% (15)
Body Mass Index, Median (95% CI)		27.1 (26.8–28.3)	27.4 (26.5–28.2)	27.5 (26.3–30.7)
Comorbidity, % (*n*)		76.9% (143)	76.3% (119)	80.0% (24)
Clavien-Dindo Classification Score, % (*n*)	0	83.9% (156)	100% (156)	–
	1	7.5% (14)	–	46.7% (14)
	2	7.5% (14)	–	46.7% (14)
	3	1.1% (2)	–	6.7% (2)
	4	–	–	–
	5	–	–	–
Any Catheter		26.7% (50)	43 (27.6%)	7 (23.3%)
Ureteral Catheter		1.6% (3)	2 (1.3%)	1 (3.3%)
JJ-Stent		14.4% (27)	22 (14.1%)	5 (16.7%)
Nephrostomy tube		11.8% (22)	20 (12.8%)	2 (6.7%)
Mortality rate, % (*n*)		11.3% (21)	10.9% (17)	13.3% (4)

positive urinary or stone culture. Of the sepsis patients, 37.5% (3/8) had negative cultures from both urine and kidney stone. Only one patient had a positive blood culture (1/8), *E. coli* with ESBL Carba in both urine and stone.

Nearly all of the patients (5/6) who developing fever postoperatively received an extra dose of intravenous aminoglycoside ($n = 4$) or carbapenem ($n = 1$) and per oral antibiotics following discharge. Looking at all complications, 12.4% (23/

186) suffered from one or more complications before being discharged from the hospital. Bleeding, defined as patients given a transfusion, occurred in 5.4% (10/186), sepsis was diagnosed in 4.3% (8/186), fever episode in 3.2% (6/186) and reoperation in 1.6% (3/186).

Of all 3.8% (7/186) of patients who sought medical care or required additional intervention within 30 days from being discharged, five of these had infectious complications, including one patient with abscess, two with pyelonephritis and two with urosepsis. One patient had hematuria and flank pain and one patient needed additional surgery (ureterolithotomy) due to residual stone.

Long-time mortality, median follow-up (range 2–9 years) postoperatively, was 11.3% (21/186) (Tables 1 and 2). Of these, 61.9% (13/21) were older than 70 years at the time of surgery and the majority, 90.5% (19/21), was diagnosed with at least one comorbidity; 52.4% (11/21) had a BMI of 25 or higher. No deaths were registered within 3 months of surgery. Median of hospital stay postoperatively was 3 days (ranging from 2 to 23 days).

Discussion

In this cohort 4.3% had sepsis and 3.2% had febrile UTI, which is in line with previous showing an incidence between 0.3 and 5% [13]. Ramaraju et al. [18] reported a SIRS incidence of 24.1% in patients given a third generation cephalosporin and aminoglycoside. Erdil et al. [19] reported a SIRS incidence of 16.7% when given antibiotics according to urinary culture preoperatively or single dose third generation cephalosporin preoperatively in the case of sterile urine. These high numbers is possibly explained by the increase of the intrarenal increased pressure during surgery, recognized by many as a source of postoperative fever. Urosepsis was seen in 1.5% patients given culture specific antibiotics or second generation cephalosporin according to Sharma et al. [13,19]. The criteria for the sepsis diagnosis has been re-evaluated recently and discrepancies in diagnosing has complicated the comparison of studies on the subject [15]. In this study, the treating doctor's encoding of sepsis in the patient chart was the deciding factor and additional data of the patient's condition was extracted to evaluate the judgment.

Our proportion of the patients having a positive urinary culture (30.1%) and stone culture (33.3%) are similar to other studies (3.2–51% and 9.4–48%, respectively) [14,20–23]. A not insignificant part of the patients had both positive urinary and stone culture. The concordance rate was 57.1%, compared to 22.6–83.3% in several studies [20–23].

Mariappan et al. [14] demonstrated a greater risk of developing urosepsis by bacteria from infected stones or pelvic urine compared with bladder urine. No such increase in risk was seen in our study, which could be explained by the fact that the current prophylactic regime works or be a consequence of the study being under powered. Having a positive urinary or stone culture, however, was an independent general risk factor for developing complications in this study. Out of the eight sepsis patients, one had a positive blood culture with the same type of bacterium in urine, stone and blood. Three patients with sepsis had negative urinary and stone cultures, this being an aseptic inflammatory response could be true but we still lack the explanation of this fever reaction and false negative cultures could still be a part of the problem. Regarding catheters one would assume that this would increase the risk of complications. This study fails to show any significant connection. Bacterial stone growth was associated with a hose connecting the external environment with the internal parts of the body namely nephrostomy or ureteral catheters. Double JJ-catheter seems to not have this effect.

In the patients with infectious complications, positive stone culture was more prevalent than a positive urine culture. This might indicate a successful eradication of bacteria in the bladder by preoperative antibiotics (not effective on the stones). Exposure to antibiotics prior to surgery could also promote development of resistant bacteria and increase the risk of sepsis [24]. Receiving antibiotics according to urinary culture increased the risk of complication, but not sepsis specifically, in this study. This is probably a result of confounding by indication, meaning that the positive urinary culture accounted for the risk and not the antibiotics *per se*. Among the patients with positive urinary culture, no advantage of giving per oral antibiotics could be seen in this study. However, these results should be interpreted with caution due to the small size of the study. Further studies should investigate the benefit of per oral antibiotics prior to

Table 2. List of comorbidities and coding.

	All patients ($n = 186$)	ICD-10 codes
Malignancy	22.0% (41)	C00–97
Diabetes mellitus	13.4% (25)	E10–14
Psychiatric disease	2.7% (5)	F04–99
Dementia	2.2% (4)	F00–03
Hypertension	27.4% (51)	I10, I15
Arrhythmia	6.5% (12)	I44–45, I47–49
Airway disease and COPD	10.2% (19)	J40–47
Bowel disease	26.3% (49)	K00–73, K75–87
Liver cirrhosis	0% (0)	K74
Urogenital disease (stone excluded)	72.6% (135)	N30–39, N40–42
Renal disease	7.5% (14)	N00–19

Table 3. Antibiotic treatment.

	All patients ($n = 186$)
Antibiotic prophylaxis (Standard Operation Procedure was Cefotaxime 1g × 2 intravenously or according to culture resistance >1 h before surgery)	100% ($n = 186$)
Preoperative per oral antibiotics according to urinary culture	13.4% ($n = 25$)
Perioperative iv antibiotics (used until nephrostomy tube was removed normally <3 days after surgery)	
Cefotaxime	78.0% (145/186)
Aminoglycoside	24.2% (45/186)
Other	2.2% (4/186)
Postoperative per oral antibiotics (used after nephrostomy tube was removed)	48.9% ($n = 91$)
Ciprofloxacin	47.3% (43/91)
Pivmecillinam	25.3% (23/91)
Other	31.9% (29/91)

Table 4. Antibiotic treatment specified.

	All patients ($n = 186$)	Complications ($n = 30$)	Positive urinary culture ($n = 56$)
Antibiotic prophylaxis	100% ($n = 186$)	100% ($n = 30$)	100% ($n = 56$)
Preoperative antibiotics according to urinary culture	13.4% ($n = 25$)	26.7% ($n = 8$)	44.6% ($n = 25$)
Preoperative antibiotics	17.7% ($n = 33$)	26.7% ($n = 8$)	44.6% ($n = 25$)
Amoxicillin	27.3% (9/33)	0	5
Ciprofloxacin	18.2% (6/33)	1	3
Pivmecillinam	18.2% (6/33)	0	2
Trimetoprim	15.2% (5/33)	1	3
Nitrofurantoin	12.1% (4/33)	0	2
Trim-Sulpha	12.1% (4/33)	0	2
Flucloxacillin	6.0% (2/33)	0	1
Cefadroxil	3.0% (1/33)	0	0
Clindamycin	3.0% (1/33)	0	0
Perioperative antibiotics	100% ($n = 186$)	100% ($n = 30$)	100% ($n = 56$)
Cefotaxime	82.8% (154/186)	23	32
Aminoglycoside	23.6% (44/186)	6	22
Cefuroxime	1.6% (3/186)	1	1
Ceftazidime	0.5% (1/186)	0	1
Meropenem	0.5% (1/186)	0	0
Piperacillin/Tazobact	0.5% (1/186)	0	0
Postoperative antibiotics	48.9% ($n = 91$)	76.7% ($n = 23$)	85.7% ($n = 48$)
Ciprofloxacin	47.3% (43/91)	2	1
Pivmecillinam	25.3% (23/91)	2	2
Nitrofurantoin	9.9% (9/91)	0	1
Amoxicillin	6.6% (6/91)	1	3
Aminoglycoside	6.6% (6/91)	7	20
Trimetoprim	5.5% (5/91)	0	5
Cefadroxil	4.4% (4/91)	0	4
Carbapenem	4.4% (4/91)	0	4
Trim-Sulfa	3.3% (3/91)	0	3
Piperacillin/Tazobact	3.3% (3/91)	0	3
Flucloxacillin	1.1% (1/91)	0	1
Other	1.1% (1/91)	0	1

surgery in order to avoid unnecessary administration of antibiotics.

The most common bacteria found in stone culture were *Enterococcus faecalis* and coagulase-negative staphylococci. Nevo et al. [25] showed bacterial resistance of 67% for second generation cephalosporins and 9% against Meropenem in *E. faecalis*. The high prevalence of *E. faecalis* must be taken into consideration. A potential strategy to minimize antibiotic use and to optimize prophylaxis would be to use a broader spectrum antibiotic, such as Piperacillin-Tazobactame as a standard, regardless of the pre-operative urinary culture. A reasonable duration would be until potential 'extra risks' catheters, namely urethral catheter and the nephrostomy, were removed, approximately 7–8 doses in all.

Richards et al. [26] reported *Enterococcus* as a frequent opportunistic pathogen in nosocomial infections and are clinically challenging to treat due to widespread resistance to antibiotics [27]. Coagulase-negative staphylococci infections are considered opportunistic and are associated with implant surgeries and immunocompromised patients [28]. Is the incidence of stone culture coagulase-negative staphylococci in this study due to sampling contamination or the presence of a nephrostomy/ureteral catheter and lacks clinical relevance? This is of course debatable, but some of the medical knowledge may indicate this. However, incidence of coagulase-negative staphylococci in renal calculi are reported by two other studies [14,29]. Of patients having bacteria in their urine preoperatively, only half received antibiotics according to culture. This can partly be explained by the proportion of mixed flora lacking bacterial resistance patterns and thereby considered to be contamination. The EAU Guidelines recommends urinary culture and treatment of all urinary infections preoperatively [10] and prophylaxis with aminoglycosides and second-generation cephalosporins. The broader spectrum antibiotics such as third-generation cephalosporins and carbapenems should be used for treatment indication only [30]. The standard perioperative drug of choice in our study was Cefotaxime, a third-generation cephalosporin. Aminoglycosides were the drug mostly used as additional iv therapy. Again, a general reflection is that none of these drugs are effective on *E. faecalis*.

The total complication rate in this cohort was 16.1%. Other complications apart from infection were bleeding, 5.4%, the need for additional surgery, 2.1%, and pain, 0.5%. Regarding the modified Dino-Clavien classification of surgical complications is not fully representative for complications in urological surgery. Therefore, there is a risk of underestimation of complications.

The population undergoing PCNL was to a large extent affected by comorbidities. This can be a result of the population's higher age compared to the normal population or a reflection of underlying diseases causing kidney stones. BMI being > 25 for the included patients may indicate that an excess of food intake could be one of the factors causing urinary stones. Taylor et al. [8] reported an association between higher BMI and increased risk of kidney stone formation.

Stone analysis shows that 92% (162/176) of stones contained calcium and the most common combination of calcium, oxalate and phosphate was found in 58.5% (103/176)

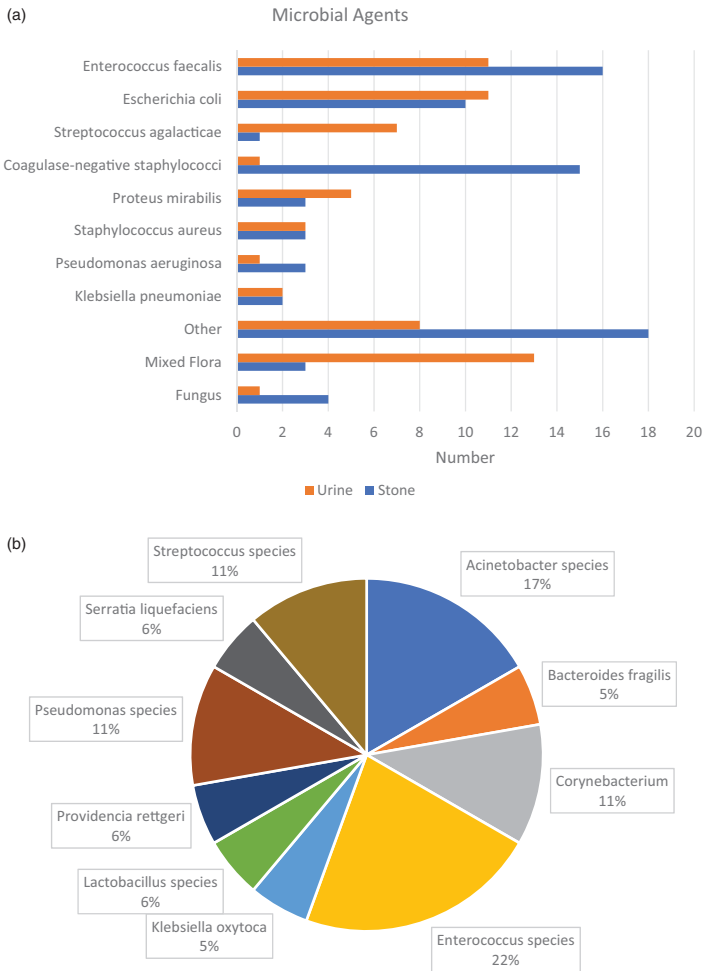


Figure 3. (a) Microbial agents in cultures of urine and stone. (b) Specification of 'other' stone microbial agents.

Table 5. Chi-square and Fisher's Exact test showing statistical significance (p-value < 0.05).

	p-value	OR	95% CI
Positive preoperative urinary culture			
To sepsis	0.678	1.716	0.371–7.942
To any complication	0.017	2.659	1.167–6.056
Positive stone culture			
To sepsis	0.135	3.187	0.735–13.817
To any complication	0.002	3.469	1.504–8.001
Preoperative antibiotic culture targeted treatment to sepsis	0.315	2.116	0.402–11.124
Preoperative antibiotics according to urinary culture to any complication			
All patients	0.008	3.713	1.447–9.527
Positive stone culture			
JJ Catheter	0.563	0.330	−0.098–0.194
To Ureteral Catheter	0.019	6.252	0.096–0.271
To Nephrostomy	<0.005	21.720	0.209–0.486
Comorbidity to any complication	0.658	1.244	0.473–3.273

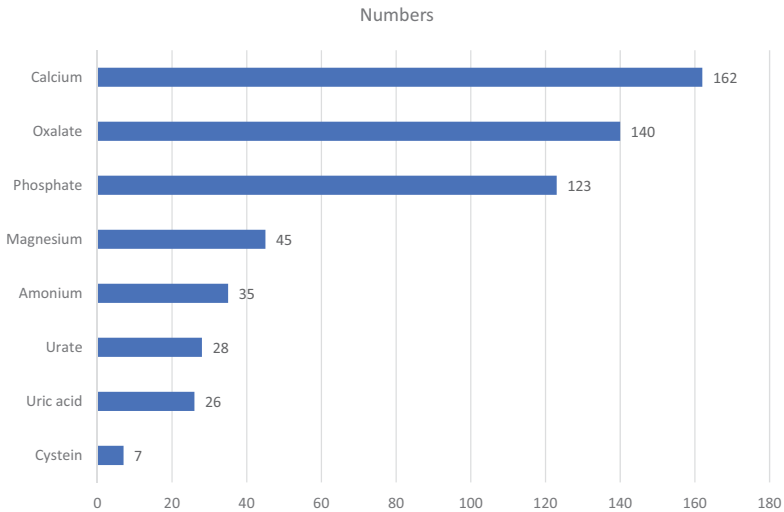


Figure 4. Stone content ($n = 186$). (Most stones containing a mix of agents and the most common mixture being Calcium/oxalate and Calcium/phosphate).

of the stones. This is substantially lower than the 80% previously reported [4]. Explanations could be a higher intake of meat and food in general, leading to a shift in stone configuration, concentrating, for example, more ammonium and uric acid in the urine.

The mortality rate in this study was 11.3%, compared to 0.9% for the total Swedish population in 2016 [31,32]. The reasonable explanations for our mortality rate are the older population and its high rate of comorbidities in the study population. No deaths were in proximity to surgery (first death 5 months after surgery).

This study has a high proportion of cultures and stone analysis taken, presenting an overview of complications and rates and provides modern information on patients undergoing PCNL. The limitation of this study is the number of patients ($n = 186$), which fails to reach statistical correlations between cultures and risk for sepsis complication.

In conclusion, positive urinary and stone cultures do not conform in all cases. Still they are seen frequently among patients undergoing PCNL and are associated with an increased risk of complications. This study has a total complication rate of 16%, of those ~10% are severe. Infectious complications stand for more than 60%. This study should be validated in a larger cohort, possibly with a higher rate of antibiotic resistance before a change of guidelines regarding prophylactic antibiotics should be proposed but if so the high prevalence of *E. faecalis* might need to be considered.

Acknowledgements

We thank the staff at the department of Urology, Helsingborg/Ängelholm hospital for helping with patient registration and Associated Professor Martins Sundqvist for contributing on bacteriological aspects of this study.

Authors' contributions

MW, MR, and AL; Sample and data collection: MW, MR. Analysis and interpretation: MW, JB, MP, AL; Drafting the manuscript for important intellectual content: MW, JB, MP, JS, and AL.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Gorthon foundation, Lions foundation, Percy Falk foundation and ALF Region Skåne.

ORCID

Magnus Wagenius http://orcid.org/0000-0002-4004-269X
Johan Stranne http://orcid.org/0000-0002-4295-6524
Adam Linder http://orcid.org/0000-0002-8187-7239

References

[1] Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2–3):e86–e96.
[2] Ljunghall S. Incidence and natural history of renal stone disease and its relationship to calcium metabolism. Eur Urol. 1978;4(6):424–430.
[3] Scales CD, Jr., Curtis LH, Norris RD, et al. Changing gender prevalence of stone disease. J Urol. 2007;177(3):979–982.
[4] Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. Nat Rev Dis Primers. 2016;2(1):16008.
[5] Segura JW. Staghorn calculi. Urol Clin North Am. 1997;24(1):71–80.
[6] Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–344.

[7] Bird VY, Khan SR. How do stones form? Is unification of theories on stone formation possible? Arch Esp Urol. 2017;70(1):12–27.
[8] Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293(4):455–462.
[9] Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005;68(3):1230–1235.
[10] Türk CK, Petrik A, Sarica K, et al. Guidelines on urolithiasis 2012. European Association of Urology; 2012 [updated February 2012]. Available from: https://uroweb.org/wp-content/uploads/20_Urolithiasis_LR-March-13-2012.pdf
[11] Wen CC, Nakada SY. Treatment selection and outcomes: renal calculi. Urol Clin North Am. 2007;34(3):409–419.
[12] Fernstrom I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10(3):257–259.
[13] Sharma K, Sankhwar SN, Goel A, et al. Factors predicting infectious complications following percutaneous nephrolithotomy. Urol Ann. 2016;8(4):434–438.
[14] Mariappan P, Smith G, Bariol SV, et al. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. J Urol. 2005;173(5):1610–1614.
[15] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–810.
[16] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–213.
[17] Labate G, Modi P, Timoney A, et al. The percutaneous nephrolithotomy global study: classification of complications. J Endourol. 2011;25(8):1275–1280.
[18] Ramaraju K, Paranjothi AK, Namperumalsamy DB, et al. Predictors of systemic inflammatory response syndrome following percutaneous nephrolithotomy. Urol Ann. 2016;8(4):449–453.
[19] Erdil T, Bostanci Y, Ozden E, et al. Risk factors for systemic inflammatory response syndrome following percutaneous nephrolithotomy. Urolithiasis. 2013;41(5):395–401.
[20] Korets R, Graversen JA, Kates M, et al. Post-percutaneous nephrolithotomy systemic inflammatory response: a prospective analysis of preoperative urine, renal pelvic urine and stone cultures. J Urol. 2011;186(5):1899–1903.
[21] Roushani A, Falahatkar S, Sharifi SH, et al. Intra-operative stone culture as an independent predictor of systemic inflammatory response syndrome after percutaneous nephrolithotomy. Urolithiasis. 2014;42(5):455–459.
[22] Shoshany O, Margel D, Finz C, et al. Percutaneous nephrolithotomy for infection stones: what is the risk for postoperative sepsis? A retrospective cohort study. Urolithiasis. 2015;43(3):237–242.
[23] Walton-Diaz A, Vinay JI, Barahona J, et al. Concordance of renal stone culture: PMUC, RPUC, RSC and post-PCNL sepsis-a non-randomized prospective observation cohort study. Int Urol Nephrol. 2017;49(1):31–35.
[24] Tandogdu Z, Cek M, Wagenlehner F, et al. Resistance patterns of nosocomial urinary tract infections in urology departments: 8-year results of the global prevalence of infections in urology study. World J Urol. 2014;32(3):791–801.
[25] Nevo A, Mano R, Shoshani O, et al. Stone culture in patients undergoing percutaneous nephrolithotomy: a practical point of view. Can J Urol. 2018;25(2):9238–9244.
[26] Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect Control Hosp Epidemiol. 2000;21(8):510–515.
[27] Miller WR, Munita JM, Arias CA. Mechanisms of antibiotic resistance in enterococci. Expert Rev Anti-Infect Ther. 2014;12(10):1221–1236.
[28] Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. Clin Microbiol Rev. 2014;27(4):870–926.
[29] Dogan HS, Guliyev F, Cetinkaya YS, et al. Importance of microbiological evaluation in management of infectious complications following percutaneous nephrolithotomy. Int Urol Nephrol. 2007;39(3):737–742.
[30] Grabe MB, Bjerklund Johansen TE, Cai T, et al. EAU guidelines on urological infections. European Association of Urology; 2013 [updated March 2015]. Available from: https://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf
[31] Statistics on Causes of Death 2016 [Internet]. Socialstyrelsen. 2017 [cited 2018 May 17]. Available from: https://www.socialstyrelsen.se/publikationer2017/2017-9-10
[32] Befolkningsstatistik i sammandrag 1960–2017 [Internet]. Statistiska centralbyrån. 2018. [cited 2018 March 21]. Available from: http://www.scb.se/hitta-statistik/statistik-efter-amne/befolkning/befolkningens-sammansattning/befolkningsstatistik/pong/tabell-och-diagram/helarsstatistik--riket/befolkningsstatistik-i-sammandrag/

Appendix 1

Grade I	Deviation from the normal postoperative course without the need for intervention
Grade II	Minor complications requiring pharmacological intervention, including blood transfusion and total parenteral nutrition
Grade IIIa and b	IIIa: Complications requiring surgical, endoscopic or radiological intervention, but self-limited, without general anesthesia IIIb: Complications requiring surgical, endoscopic radiological intervention, but self-limited, with general anesthesia
Grade IVa and b	IVa: Life threatening complications requiring intensive care unit management; single organ dysfunction, including dialysis IVb: Life threatening complications requiring intensive care unit management; multiorgan dysfunction
Grade V	Death of a patient

The CROES modified Clavien-Dindo Classification [17,18], for classifying surgical complications.

Paper IV

Factors influencing stone-free rate of Extracorporeal Shock Wave Lithotripsy (ESWL); A cohort study

[.b] Magnus Wagenius MD, [b] Karl Oddason MD, [b] Maria Utter MD, [c] Marcin Popiolek MD, [a, b] Andreas Forsvall MD, [c]Karl-Johan Lundström, [a]Adam Linder MD, PhD

[a] Department of Clinical Sciences, Division of Infection Medicine, Lund University, Lund Sweden. [b] Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden [c] Department or Urology, Örebro University Hospital, Örebro, Sweden. [c] Institution of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden

Key Words: Extracorporeal shock-wave lithotripsy, monotherapy, infection, Stone Free Rate, outcome, ureteric stone, ureteroscopy.

Correspondence: Magnus Wagenius Department of Surgery, Helsingborg Hospital, Sweden.

magnus.wagenius@gmail.com

Abstract

Objective: To evaluate the success rate of Extracorporeal Shock Wave Lithotripsy (ESWL) therapy and identify relevant treatment-specific factors affecting stone-free rate (SFR) after ESWL.

Material and methods: All ESWL treatments in the years 2016-2019, in Ängelholm Hospital, Skåne, Sweden were analysed retrospectively. Primary outcome was successful ESWL treatment, defined as stone-free rate (SFR) at 3 months. Univariate logistic regression was used followed by multivariable regression. Lasso analysis was made to adjust for treatment-specific factors such as age, stone size, skin-to-stone distance (SSD), mean attenuation value (MAV), number of treatments, stone location, and presence of a urinary stent.

Results: Factors affecting successful ESWL treatment were age ($p<0.001$), stone size and volume (both $p=0.001$). SSD, MAV, sex, laterality and drainage did not have an effect on SFR in this study. After one ESWL treatment session, 46.7% of the patients were stone-free.

Conclusion: The results of this study indicate that stone size and age are the most predictive factors for ESWL outcome. We present a simple model for prediction of SFR after ESWL, using stone size and age. This could be used when counselling patients before ESWL treatment.

Introduction

Renal colic, caused by urolithiasis, accounts for 1% of emergency department (ED) visits in Europe [1, 2]. Treatment of urolithiasis includes ureteroscopy (URS), extracorporeal shock wave lithotripsy (ESWL), and percutaneous nephrolithotomy (PCNL). The European Association of Urology (EAU) recommends the use of URS and ESWL for removal of ureteric stones [3]. International guidelines usually divide stones into three groups, depending on size (<10 mm, 10–20 mm, and >20 mm). ESWL is currently an important part of urolithiasis treatment [4]. ESWL can be recommended for all stones smaller than 20 mm.

ESWL is more cost efficient and clinically effective compared to URS, when treating renal stones <10 mm [3, 5]. ESWL does not require general anaesthesia and is an out-patient procedure which makes it cost efficient and also preferable with regard to infectious diseases. The COVID-19 pandemic has decreased operative availability in many places worldwide making ESWL sometimes the only alternative for urolithiasis treatment [6].

A factor affecting the success of ESWL-treatment includes the technical equipment used, but patient- and stone-related factors also play a central role for the outcome or stone free rate (SFR). SFR is measured as the proportion of patients with residual stone fragments smaller than 4mm after a full course of ESWL treatment (up to 3 ESWL procedures). Factors previously shown to have an impact on SFR are stone size, skin to stone distance (SSD), radiodensity and possibly the presence of a ureteric stent before ESWL[3, 5, 7-9]. The type of ESWL machine also affects the SFR, and most the important factors seem to be the focal zone and type of shockwave generator [10]. Other factors that play a role are the frequency of shock waves (Hz) and power ramping [11]. One of the problematic issues with stone studies is that the follow-up method varies. Some use ultrasound or a plain X-ray of the kidney, ureter and bladder (KUB), which is not as accurate as non-contrast-enhanced computed tomography (NCCT). Many

studies are also relatively small and the treatment strategy after an unsuccessful ESWL is often unclear.

The aim of this study is to identify easily accessible and objective factors known before ESWL that influence the SFR of ESWL treatment.

Materials and Methods

This retrospective study included all patients treated with ESWL in the years 2016-2019, at the Urolithiasis Centre of Ängelholm hospital in Skåne County, Sweden. The centre serves approximately 450 000 inhabitants in the north-western part of Skåne regarding stone treatment. The ESWL machine used was Stortz lithotripter MODULITH® SLX-F2, 3rd generation with electromagnetic shockwave generator and dual focus option. Treatment was performed under X-ray monitoring. EAU Guidelines and contraindications for ESWL treatment were followed [3, 12]. We followed Stortz Medical's recommendations regarding the number of shockwaves and energy level. Power ramping was routinely performed during the study period and 1.5 Hz was routinely used. Patients with diabetes, a positive urine culture or dipstick test, an indwelling stent, or a catheter were given antibiotic prophylaxis (Ciprofloxacin 500 mg) orally approximately 30 minutes before ESWL [3, 12, 13].

Stones 6 mm or larger causing obstruction or symptoms were considered a treatment indication. All patients were presented the option of ESWL. The stone-treating doctor, in consensus with the patient, decided on ESWL as the treatment modality. Pre-ESWL stenting was not done routinely. Pre-treatment stenting was due to obstruction or pain, and rarely due to stone size alone. Patients with stones 6 mm or larger, visualized on CT scout image and located in the upper 2/3 of the ureter or the kidney pelvis, were recommended ESWL.

All patients were evaluated before and after ESWL with NCCT. Follow up with NCCT was done 3-4 weeks after treatment. Fragmentation was assessed as either 1) complete fragmentation/successful treatment (stone size < 4 mm), 2) partial fragmentation (stone size 4-5 mm), and 3) incomplete fragmentation (stone size ≥ 6 mm). This study defines SFR patients with residual stone fragments ≤4mm Complete fragmentation was not followed up further. Partial fragmentation was followed up with an annual NCCT. Incomplete fragmentation was generally re-treated with ESWL up to three times in total, whereafter another modality was chosen. The modern CT protocol is now standardized by the urological radiographic society in Sweden using 120 kV and 3/1.5 mm [14], but the standardized protocol was not in use at this time. NCCT was optimized individually regarding kV. Normally 3/2 mm in three planes was used, making reconstruction possible with 1 mm thickness and 0.8 mm intervals, thus detecting all but very small and insignificant stones. When measuring Hounsfield density (HU) and using the "region of interest" (ROI) measurement we included 2/3 of the stone to avoid partial volume effects. Two consultants in urology measured all stones. The measurements were performed in the same way and inter-operator differences is presented in a Bland-Altman diagram (fig. 1).

This study was approved by the local ethics committee at Lund University (Dnr. 2016/254).

Data gathered prospectively included the number of ESWL treatments, presence of an indwelling stent, stone location (kidney, upper ureter, lower ureter), number of shockwaves, shockwave frequency, energy level and use of prophylactic antibiotics. Data were entered when treating the patients and stored in a computerized medical chart system (Melior).

Data gathered retrospectively included complementary treatment modalities (URS, PCNL or percutaneous nephrostomy), stone size (measured three dimensionally with the largest size documented), radiodensity in HU (measured on CT, two different points were measured and a mean value of these two points was calculated) and SSD (measured as the length from stone to skin at the outer border of psoas/paraspinal muscles or, when in prone position, the shortest

measure from the abdominal side of the skin). We excluded patients with any stone larger than 2cm.

Statistics

Patient and stone specific factors were analysed with both univariate analyses (Chi-squared or t-test comparing patients with successful treatment to those with unsuccessful treatment) and multivariate analyses (logistic and lasso regression) to evaluate if they were significant independent factors. Subgroup analyses was also made looking at first and second treatment analysing differences in factors affecting SFR. The data was randomly split into two datasets of equal size, which we refer to as "training data" and "test data" for the analysis. Lasso analysis stands for "least absolute shrinkage and selection operator". It is a regression analysis method that performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the resulting statistical model. Using the training data, we applied lasso regression to select the best predictors. The lambda-value for the lasso regression was chosen using cross validation. The results are presented as odds ratios with 95% confidence intervals and p-values. Then the selected model was evaluated using the test data and using receiver operating characteristic (ROC) curves to calculate the area under the curve (AUC). Statistical analysis was performed using computations in R: A Language and Environment for Statistical Computing version 4.0.2.

Results

During the study period, 727 ESWL treatments were performed. Three treatments (0.4%) were excluded from the study (patient's death or mandatory follow up was not performed). We excluded 17 treatments on stones > 2 cm, leaving 707 treatments (patients treated one to three times) for evaluation. When analysing all data the cohort was randomly split into two equally large groups to minimise the risk of assumption bias.

Patient characteristics

Patient characteristics are presented in table 1. The majority (714 (98.9%)) received small focus shock waves. The median machine energy level/power was 6 in 562 (77.5%) of the treatments. The median shock wave frequency was 1.5 Hz, used in 712 (98.3%) of treatments. During the ESWL 19% had a drainage (14.5% pigtail and 4.5% nephrostomy). The mean age in the study population was 61 years and the mean stone density measured in HU was 936. 83% had their stone located in the renal pelvis, leaving only 17% of the stones located in the ureter. The cohort in this study had a low percentage of ureteric stones, but we found no significant correlation between location and SFR after ESWL treatment (p=0.78).

Stone free rate (SFR)

Successful ESWL treatment (residual stone ≤ 4 mm and no re-intervention needed) was achieved in 333 (46 %) treatments. On the follow up using NCCT, 143 patients (19.8%) had 4-5 mm stones and 247 (34.1%) had residual stones ≥ 6 mm. Patients with residual stones ≥ 6 mm were either followed by NCCT or they received an additional ESWL treatment or

treatment by another modality. The ability of the various baseline variables to predict a successful treatment outcome (stones ≤4 mm) was examined using both univariate (Chi-squared or t-test) and multivariable logistic regression. In order to determine which baseline variables are associated with treatment success, we first performed a univariate analysis with each variable of interest (table 3). We found that age ($p<0.001$), maximum size ($p<0.001$), ($p<0.001$), volume and SSD ($p=0.047$) was significantly correlated to treatment success.

Next, the multivariate analysis was performed (table 4). In this analysis we chose to include volume (excluding max size showing the same result) showing significance on only age and volume (both $p<0.001$). Using a lasso regression model (tables 4-5) verifying that age and both max size and volume are strongly associated to SFR ($p<0.001$). The subgroups of patients receiving their first and second treatment were analysed separately (tables 7 and 8 respectively). We found that, at the first treatment session, both age and max size were significantly affecting SFR ($p<0.001$). In this material we investigated correlations between the possible predictors of SFR presented in table 9. No strong correlation was seen.

To investigate the interindividual measure difference between the two consultants a one sample T-test was performed. Approximately 10% of patients were randomly chosen to measure differences in measurement. There were no significant differences in maximum size or SSD measurements. There was a significant difference in HU measurements. A Bland-Altman diagram of differences in max size is presented in figure 1.

A ROC curve is presented in Fig. 2. The full model including SSD, HU, maximum size had an AUC of 0.72, while a model that included age and either maximum size or volume had an AUC of 0.74. Both maximum size and volume correlate strongly to each other and therefor only one of these were included in the model for further analysis. We focused on maximum size, believing that this figure is easier to work with (as it does not require an extra step of calculating the volume) for both the radiologist and the treating urologist.

Finally, we then used the most predictive factors identified in the above models to create an equation for calculation of odds and probability of being stone-free after up to three ESWL sessions. We suggest the following equation to calculate odds for success:

$$84.04 * 0.954^{\text{Age}} * 0.851^{\text{Size}}$$

Calculation of probability (p) can be made through:

$$P = \frac{odds}{1 + odds}$$

In figure 3 we present a visual diagram predicting SFR/treatment success with age and max stone size as objective factors.

Discussion

This study found that younger age and smaller stones were predictors of success when performing ESWL. It is only valid for stone sizes below 2 cm as patients with stones above 2cm were excluded from the cohort.

The aim of the study was to identify factors affecting the SFR following ESWL treatment. Factors that might influence the treatment decision should be easily available and understandable both to the patient and the treating physician. In this retrospective study we examined several factors that might affect the SFR of ESWL which are readily available prior to treatment. We conclude that measurements of size and SSD seems rather consistent between different investigators. HU measurement seems more difficult and interindividual differences were found when measuring this parameter.

It is well known and accepted that smaller stone size has an effect on spontaneous stone passage [15, 16]. It is conceivable that more data about the stone and the patient could better predict SFR. Our data suggests that the largest size together with age are the best and strongest predictors of SFR and thus might be sufficient for prediction of treatment success. The parameters are easily accessible and can be used when calculating odds or probability of a successful treatment. Size, measured as the maximal diameter in millimetres, and volume are equally associated with SFR.

We found that younger age was a significant predictor of successful ESWL, a finding shown previously in other studies [17-22]. A weakness regarding age in this study is that the follow-up for measuring SFR is 3 months. It has been shown that the age effect is reduced if the follow-up is longer (>24 months) [23]. Age being such a strong predictor of SFR after ESWL treatment could influence clinical practice. The mean age in our study population is 61 years. We know from other studies that the peak age for stone disease in our part of the world is between 40 and

50 years [24], indicating that in this cohort there was a tendency to choose ESWL for the more fragile elderly patients, which could affect our results. We found a very strong association between younger age and a higher chance of becoming stone-free after ESWL treatment. Although the underlying mechanisms remain unknown it is suggested that sclerotic changes in the renal parenchyma occur with aging, leading to increased acoustic impedance and poor fragmentation, and consequently low SFR after ESWL therapy for kidney calculi [18, 19]. It may also be due to a physiologic effect that humans easier pass stones when they are young, or due to the reduced urine volume of older patients. Human activity reduces with ageing. Elderly people spend less time standing up and they don't move around as much, reducing the gravitational effect that normally pushes the stone downward through the urinary tract. Sexual activity varies and is reduced with age, and a previously study shows that sexual activity has a positive effect on SFR after ESWL [25]. Finally, it is possible that there was a selection bias in our cohort, with simpler stone cases being present in the younger patients and complex cases in older groups being preferentially chosen for ESWL treatment. We unfortunately cannot check this possibility in this cohort since data on PCNL and URS during this period is lacking.

Stone size was the other factor that was strongly associated with higher SFR after ESWL in the current study. Multiple studies have shown that bigger stones have a lower SFR, as SFR is defined as fragments less than 4mm [11, 15, 26, 27]. Stone size as a predictor of SFR, or successful treatment, seems to unite most studies on outcome after ESWL. Other factors such as skin to stone distance (SSD), body-mass index (BMI), Hounsfield units (HU), and even location seem to vary between studies investigating SFR after ESWL.

We expected that radiodensity (HU) could be a factor affecting SFR results. We did not find any significant association between HU and SFR. Previous studies have found that a density value below 600 – 1000 HU relates positively to SFR [7, 28-39]. These studies vary in their mean HU value, but most had a lower mean HU value than our cohort. One other study, the

Mullhaupt study, did not find a correlation between HU [40]. The mean HU in the Mullhaupt study (957 HU) is more comparable to ours . We find that HU is difficult measuring in a consistent way. HU in our study was measured by only two people, which should make it easier to do the measurements in a systematic way. Even so, in this study we find that the interindividual difference in HU measurement turn out significant (when testing the measure differences against the null-hypothesis with a T-test). It is not always clear in studies exactly how many people are involved in the X-ray measurements, and interindividual measure differences are rarely accounted for, which we think could be a major source of error in HU values. The cohort in this study had a relatively high mean HU value of 936, which could have an effect on SFR of the group as a whole. It is however also a possibility that the association of HU with SFR in other studies could be caused simply by age or size. In this study HU correlates to both age and maximum stone size but stronger to size.

SSD was also a predictor of SFR in several studies [8, 35, 40, 41], apart from one study that showed no clear correlation [28]. The cut off value for a successful treatment in these studies ranges from 9-11 cm. Theoretically, the shorter the SSD the better the SFR because the ESWL machine is closer to the stone and less energy is absorbed by the tissues. We used a more pragmatic way of measuring the SSD compared to other studies. SSD was measured from the skin, directed towards the stone passing on the edge of the psoas/paraspinal muscles. Studies normally use measurements from 0°,45°, and 90°, calculating a mean of these three values or the value at 45°, presented as SSD. In the univariate analysis we found a significant association of SSD with SFR, however in the more complex multivariate logistic regression and lasso regression analyses this effect disappeared. This indicates that the SSD, using our method of measurement, is linked to the other strongly significant factors affecting SFR that we identified in this study, namely age and size. We believe it is most likely that SSD is linked to size even

if the correlation we find is not a strong one (table 9). This study therefore did not confirm that SSD is an important factor for SFR after ESWL.

Indwelling stents cause bothersome symptoms for many patients. The positive effect of reducing stone-related symptoms after ESWL are of limited and debated value, both in terms of complications and SFR. The need for acute treatment for “Steinstrasse”, a complication after ESWL, is reduced by stenting but the need for complementary treatments is not reduced [42, 43]. One confounding factor for the effects of stenting is that patients who receive indwelling stents have larger stones and/or symptoms from them [42-44]. This study found no correlation between preoperative stenting and maximum stone size and showed no effect of ureteral stenting on SFR after ESWL. Hirsh et al. found that indwelling ureteral stents decrease SFR, contemplating that stents can absorb shock waves like Goel et al. suggested previously [8, 45]. In this material SFR was not significantly affected by any stenting.

Stone location also could affect SFR. Distal stones tend to have higher SFR after ESWL compared to other locations [11]. Hirsch et al. showed that stone size tends to be larger in the renal pelvis and thereby a possible confounding factor as stone location could simply reflect stone size [8].

There is a clear lack of consensus on how to evaluate a successful ESWL treatment. We choose to define successful treatment as having residual stones ≤ 4 mm and we used this definition when calculating SFR. Most studies use a stone size ≤ 4 mm, but one could choose a smaller measurement like < 3mm as discussed in some studies [7, 28, 36, 37, 45]. Proposals for a new definition of SFR have been suggested [46]. Standard practice at the hospital during this study was to wait for natural stone passage if the stone fragments after ESWL were < 6 mm, and therefore normally no further treatment was applied to these residual stones. Stones in the ureter were followed closely with NCCT until passage. Stones < 6 mm in the renal pelvis were recommended follow up with yearly NCCT to evaluate potential growth. The SFR in this study

after one ESWL treatment was 46%, corresponding well to another study where retreatment was needed in up to 50% of patients [20] in order to reach a typical SFR of 70-80% [3, 11].

Finding outcome predictors for ESWL has been the aim of many research groups, ours included. Technical development and the increased use of NCCT now delivers more data that can be used in preoperative decision-making regarding treatment modality and approach. It may also give us the tools to better predict SFR after treatment. It is even possible that the number of treatments needed for the patient to become stone free could be predicted. Jendeberg et al. presented a predictive model for the natural passage of stones based on size and stone location [15].

Hirsch et al. recently published an article focusing on SFR prediction [8] and a number of studies focus on identifying all prognostic factors that affect ESWL results [7, 8, 47-50]. Hirsch et al. presented a predictive model that includes variables that many prior studies found to be significant when predicting treatment success and suggested cut-off values for each (≤987 HU, stone size ≤11 mm and SSD (45 degrees) ≤ 88 mm). The AUC of their model using these three predictors had an AUC of 0.74, which is exactly the same as the AUC of our model (0.74) using age and maximum size. We therefore have presented a predictive model that we believe to be a valuable tool in clinical everyday practice. It is a simple model using age and stone size to calculate SFR after ESWL. An example calculation is shown in fig 2.

A possible weakness of this study is the retrospective design. Additionally, the inclusion criteria in this cohort (only including patients receiving ESWL) allowed us to look at ESWL treatment alone but made it impossible to compare to other stone treatments. SSD was not measured as a contemporary series and HU was measured by two consultants. A strength of the study was the inclusion of a sufficient sample size for multivariate analysis. Additionally, all ESWL treatments included in our study were evaluated with NCCT before and after treatment. Using NCCT makes the judgement of SFR more reliable than ultrasound or plain X-ray [3].

Conclusion

The results of this study indicate that stone size and age are the most important factors for predicting SFR after ESWL. Stone attenuation (HU) and skin to stone distance (SSD) did not significantly affect the SFR following ESWL treatment in this study. With this work we present a simple equation for the calculation of SFR after ESWL that may contribute to the counselling of stone patients in the future.

References

1. Brown J. Diagnostic and treatment patterns for renal colic in US emergency departments. Int Urol Nephrol. 2006;38(1):87-92. Epub 2006/02/28. doi: 10.1007/s11255-005-3622-6. PubMed PMID: 16502058.
2. Cupisti A, Pasquali E, Lusso S, et al. Renal colic in Pisa emergency department: epidemiology, diagnostics and treatment patterns. Intern Emerg Med. 2008;3(3):241-4. Epub 2008/04/26. doi: 10.1007/s11739-008-0145-z. PubMed PMID: 18437291.
3. C. Türk (Chair) AN, A. Petřík, C. Seitz, A. Skolarikos (Vice-chair), B. Somani, K. Thomas, G. Gambaro (Consultant nephrologist), Guidelines Associates: N.F. Davis JFD, R. Lombardo, L. Tzelves. EAU Guidelines on Urolithiasis 2021. Available from: https://uroweb.org/guideline/urolithiasis/.
4. Zumstein V, Betschart P, Abt D, et al. Surgical management of urolithiasis - a systematic analysis of available guidelines. BMC Urol. 2018;18(1):25. Epub 2018/04/11. doi: 10.1186/s12894-018-0332-9. PubMed PMID: 29636048; PubMed Central PMCID: PMCPMC5894235.
5. NICE Guideline - Renal and ureteric stones: assessment and management: NICE (2019) Renal and ureteric stones: assessment and management. BJU Int. 2019;123(2):220-32. Epub 2019/01/19. doi: 10.1111/bju.14654. PubMed PMID: 30656839.
6. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020;396(10243):27-38. Epub 2020/06/02. doi: 10.1016/s0140-6736(20)31182-x. PubMed PMID: 32479829; PubMed Central PMCID: PMCPMC7259900.
7. El-Nahas AR, El-Assmy AM, Mansour O, et al. A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock wave lithotripsy: the value of high-resolution noncontrast computed tomography. European urology. 2007;51(6):1688-93; discussion 93-4. Epub 2006/12/13. doi: 10.1016/j.eururo.2006.11.048. PubMed PMID: 17161522.
8. Hirsch B, Abt D, Gusewell S, et al. Outcome groups and a practical tool to predict success of shock wave lithotripsy in daily clinical routine. World J Urol. 2021;39(3):943-51. Epub 2020/05/22. doi: 10.1007/s00345-020-03253-5. PubMed PMID: 32436072.
9. Assimos D, Krambeck A, Miller NL, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016;196(4):1153-60. Epub 2016/05/31. doi: 10.1016/j.juro.2016.05.090. PubMed PMID: 27238616.
10. Grenabo L, Lindqvist K, Adami HO, et al. Extracorporeal shock wave lithotripsy for the treatment of renal stones. Treatment policy is as important for success as type of lithotriptor and patient selection. Arch Surg. 1997;132(1):20-6; discussion 7. PubMed PMID: 9006548.
11. Wagenius M, Jakobsson J, Stranne J, et al. Complications in extracorporeal shockwave lithotripsy: a cohort study. Scand J Urol. 2017;51(5):407-13. Epub 2017/08/05. doi: 10.1080/21681805.2017.1347821. PubMed PMID: 28770662.
12. Türk C NA, Petrik A, Seitz C, Skolarikos A, Thomas K. EAU Guidelines on Urolithiasis 2020. . European Association of Urology Guidelines 2019 Edition. 2020.
13. Lu Y, Tianyong F, Ping H, et al. Antibiotic prophylaxis for shock wave lithotripsy in patients with sterile urine before treatment may be unnecessary: a systematic review and meta-analysis. J Urol. 2012;188(2):441-8. doi: 10.1016/j.juro.2012.04.014. PubMed PMID: 22704118.
14. Dahlman P, Dahlman PC, Akademiska sjukhuset U, et al. Rekommendationer för mätning av urinvägskonkrement/SURF:s kontrastmedelsgrupp, Version 1.0/2021-03-16. 2021.
15. Jendeberg J, Geijer H, Alshamari M, et al. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. Eur Radiol. 2017;27(11):4775-85. Epub 2017/06/09. doi: 10.1007/s00330-017-4852-6. PubMed PMID: 28593428; PubMed Central PMCID: PMCPMC5635101.
16. Yallappa S, Amer T, Jones P, et al. Natural History of Conservatively Managed Ureteral Stones: Analysis of 6600 Patients. J Endourol. 2018;32(5):371-9. Epub 2018/02/28. doi: 10.1089/end.2017.0848. PubMed PMID: 29482379.

17. Ichiyanagi O, Nagaoka A, Izumi T, et al. Age-related delay in urinary stone clearance in elderly patients with solitary proximal ureteral calculi treated by extracorporeal shock wave lithotripsy. Urolithiasis. 2015;43(5):419-26. Epub 2015/05/20. doi: 10.1007/s00240-015-0783-3. PubMed PMID: 25981235.
18. Ng CF, Wong A, Tolley D. Is extracorporeal shock wave lithotripsy the preferred treatment option for elderly patients with urinary stone? A multivariate analysis of the effect of patient age on treatment outcome. BJU Int. 2007;100(2):392-5. Epub 2007/04/17. doi: 10.1111/j.1464-410X.2007.06909.x. PubMed PMID: 17433030.
19. Ng CF. The effect of age on outcomes in patients undergoing treatment for renal stones. Curr Opin Urol. 2009;19(2):211-4. Epub 2009/02/07. doi: 10.1097/mou.0b013e32831e16b7. PubMed PMID: 19195134.
20. Abdel-Khalek M, Sheir KZ, Mokhtar AA, et al. Prediction of success rate after extracorporeal shock-wave lithotripsy of renal stones--a multivariate analysis model. Scand J Urol Nephrol. 2004;38(2):161-7. Epub 2004/06/19. doi: 10.1080/00365590310022626. PubMed PMID: 15204407.
21. Abdel-Khalek M, Sheir K, Elsobky E, et al. Prognostic factors for extracorporeal shock-wave lithotripsy of ureteric stones--a multivariate analysis study. Scand J Urol Nephrol. 2003;37(5):413-8. Epub 2003/11/05. doi: 10.1080/00365590310006255. PubMed PMID: 14594691.
22. Wiesenthal JD, Ghiculete D, Ray AA, et al. A clinical nomogram to predict the successful shock wave lithotripsy of renal and ureteral calculi. J Urol. 2011;186(2):556-62. Epub 2011/06/21. doi: 10.1016/j.juro.2011.03.109. PubMed PMID: 21684557.
23. Christian C, Thorsten B. The preferred treatment for upper tract stones is extracorporeal shock wave lithotripsy (ESWL) or ureteroscopic: pro ESWL. Urology. 2009;74(2):259-62. Epub 2009/08/04. doi: 10.1016/j.urology.2008.08.522. PubMed PMID: 19646607.
24. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2-3):e86-96. PubMed PMID: 20811557; PubMed Central PMCID: PMCPMC2931286.
25. Li W, Mao Y, Lu C, et al. Role of Sexual Intercourse after Shockwave Lithotripsy for Distal Ureteral Stones: A Randomized Controlled Trial. Urol J. 2020;17(2):134-8. Epub 2020/03/18. doi: 10.22037/uj.v0i0.5400. PubMed PMID: 32180212.
26. Polat F, Yesil S, Ak E, et al. Safety of ESWL in elderly: evaluation of independent predictors and comorbidity on stone-free rate and complications. Geriatr Gerontol Int. 2012;12(3):413-7. Epub 2012/01/04. doi: 10.1111/j.1447-0594.2011.00781.x. PubMed PMID: 22212400.
27. Abdelghany M, Zaher T, El Halaby R, et al. Extracorporeal shock wave lithotripsy of lower ureteric stones: Outcome and criteria for success. Arab J Urol. 2011;9(1):35-9. Epub 2011/03/01. doi: 10.1016/j.aju.2011.03.010. PubMed PMID: 26579265; PubMed Central PMCID: PMCPMC4149054.
28. Nakasato T, Morita J, Ogawa Y. Evaluation of Hounsfield Units as a predictive factor for the outcome of extracorporeal shock wave lithotripsy and stone composition. Urolithiasis. 2015;43(1):69-75. Epub 2014/08/21. doi: 10.1007/s00240-014-0712-x. PubMed PMID: 25139151.
29. Wiesenthal JD, Ghiculete D, John D'A Honey R, et al. Evaluating the importance of mean stone density and skin-to-stone distance in predicting successful shock wave lithotripsy of renal and ureteric calculi. Urological Research. 2010;38(4):307-13. doi: 10.1007/s00240-010-0295-0.
30. Yoshida S, Hayashi T, Ikeda J, et al. Role of volume and attenuation value histogram of urinary stone on noncontrast helical computed tomography as predictor of fragility by extracorporeal shock wave lithotripsy. Urology. 2006;68(1):33-7. Epub 2006/06/30. doi: 10.1016/j.urology.2006.01.052. PubMed PMID: 16806419.
31. Pareek G, Armenakas NA, Fracchia JA. Hounsfield units on computerized tomography predict stone-free rates after extracorporeal shock wave lithotripsy. J Urol. 2003;169(5):1679-81. Epub 2003/04/11. doi: 10.1097/01.ju.0000055608.92069.3a. PubMed PMID: 12686807.
32. Wang L-J, Wong Y-C, Chuang C-K, et al. Predictions of outcomes of renal stones after extracorporeal shock wave lithotripsy from stone characteristics determined by unenhanced helical

computed tomography: a multivariate analysis. European Radiology. 2005;15(11):2238-43. doi: 10.1007/s00330-005-2742-9.
33. Gupta NP, Ansari MS, Kesarvani P, et al. Role of computed tomography with no contrast medium enhancement in predicting the outcome of extracorporeal shock wave lithotripsy for urinary calculi. BJU International. 2005;95(9):1285-8. doi: https://doi.org/10.1111/j.1464-410X.2005.05520.x.
34. JOSEPH P, MANDAL AK, SINGH SK, et al. Computerized Tomography Attenuation Value of Renal Calculus: Can It Predict Successful Fragmentation of the Calculus by Extracorporeal Shock Wave Lithotripsy? A Preliminary Study. Journal of Urology. 2002;167(5):1968-71. doi: doi:10.1016/S0022-5347(05)65064-1.
35. Ng C-F, Siu DY-W, Wong A, et al. Development of a Scoring System From Noncontrast Computerized Tomography Measurements to Improve the Selection of Upper Ureteral Stone for Extracorporeal Shock Wave Lithotripsy. Journal of Urology. 2009;181(3):1151-7. doi: doi:10.1016/j.juro.2008.10.161.
36. Perks AE, Schuler TD, Lee J, et al. Stone Attenuation and Skin-to-Stone Distance on Computed Tomography Predicts for Stone Fragmentation by Shock Wave Lithotripsy. Urology. 2008;72(4):765-9. doi: 10.1016/j.urology.2008.05.046.
37. Tanaka M, Yokota E, Toyonaga Y, et al. Stone Attenuation Value and Cross-Sectional Area on Computed Tomography Predict the Success of Shock Wave Lithotripsy. Korean J Urol. 2013;54(7):454-9.
38. Pareek G, Armenakas NA, Panagopoulos G, et al. Extracorporeal shock wave lithotripsy success based on body mass index and Hounsfield units. Urology. 2005;65(1):33-6. Epub 2005/01/26. doi: 10.1016/j.urology.2004.08.004. PubMed PMID: 15667858.
39. Ouzaid I, Al-qahtani S, Dominique S, et al. A 970 Hounsfield units (HU) threshold of kidney stone density on non-contrast computed tomography (NCCT) improves patients' selection for extracorporeal shockwave lithotripsy (ESWL): evidence from a prospective study. BJU Int. 2012;110(11 Pt B):E438-42. doi: 10.1111/j.1464-410X.2012.10964.x. PubMed PMID: 22372937.
40. Mullhaupt G, Engeler DS, Schmid HP, et al. How do stone attenuation and skin-to-stone distance in computed tomography influence the performance of shock wave lithotripsy in ureteral stone disease? BMC urology. 2015;15:72. Epub 2015/07/24. doi: 10.1186/s12894-015-0069-7. PubMed PMID: 26201514; PubMed Central PMCID: PMCPMC4511972.
41. Patel T, Kozakowski K, Hruby G, et al. Skin to stone distance is an independent predictor of stone-free status following shockwave lithotripsy. J Endourol. 2009;23(9):1383-5. Epub 2009/08/22. doi: 10.1089/end.2009.0394. PubMed PMID: 19694526.
42. Ather MH, Shrestha B, Mehmood A. Does ureteral stenting prior to shock wave lithotripsy influence the need for intervention in steinstrasse and related complications? Urologia internationalis. 2009;83(2):222-5. doi: 10.1159/000230028. PubMed PMID: 19752621.
43. Musa AA. Use of double-J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. International urology and nephrology. 2008;40(1):19-22. doi: 10.1007/s11255-006-9030-8. PubMed PMID: 17394095.
44. Madbouly K, Sheir KZ, Elsobky E, et al. Risk factors for the formation of a steinstrasse after extracorporeal shock wave lithotripsy: a statistical model. J Urol. 2002;167(3):1239-42. PubMed PMID: 11832705.
45. Goel H, Gahlawat S, Bera M, et al. Role of clinical and radiological parameters in predicting the outcome of shockwave lithotripsy for ureteric stones. Urology Annals. 2018;10(2):159-64. doi: 10.4103/ua.Ua_84_17.
46. Somani BK, Desai M, Traxer O, et al. Stone-free rate (SFR): a new proposal for defining levels of SFR. Urolithiasis. 2014;42(2):95. Epub 2013/12/10. doi: 10.1007/s00240-013-0630-3. PubMed PMID: 24317839.
47. Petrides N, Ismail S, Anjum F, et al. How to maximize the efficacy of shockwave lithotripsy. Turk J Urol. 2020;46(Supp. 1):S19-S26. Epub 2020/11/03. doi: 10.5152/tud.2020.20441. PubMed PMID: 33135997; PubMed Central PMCID: PMCPMC7731956.

48. Tokas T, Habicher M, Junker D, et al. Uncovering the real outcomes of active renal stone treatment by utilizing non-contrast computer tomography: a systematic review of the current literature. World J Urol. 2017;35(6):897-905. doi: 10.1007/s00345-016-1943-y. PubMed PMID: 27738806.
49. Knoll T, Buchholz N, Wendt-Nordahl G. Extracorporeal shockwave lithotripsy vs. percutaneous nephrolithotomy vs. flexible ureterorenoscopy for lower-pole stones. Arab J Urol. 2012;10(3):336-41. doi: 10.1016/j.aju.2012.06.004. PubMed PMID: 26558046; PubMed Central PMCID: PMCPMC4442916.
50. Abdel-Khalek M, Sheir KZ, Mokhtar AA, et al. Prediction of success rate after extracorporeal shock-wave lithotripsy of renal stonesA multivariate analysis model. Scandinavian Journal of Urology and Nephrology. 2004;38(2):161-7. doi: 10.1080/00365590310022626.

Table 1. Patient characteristics (stones >2 cm not excluded) (n=707 treatments).

Variable	**Mean ± standard deviation**	**Median (range)**
Radiodensity (HU)	939 ± 271	940 (100-1900)
SSD (cm)	10.5 ± 2.5	10.4 (5-19)
Largest stone size (mm)	10.2 ± 3.4	9 (6-19)
Age (years)	60.7± 15.1	62 (20-99)
	Number (% of treatments)	
Stone location		
- Calyces	181 (25.6%)	
- Renal pelvis	402 (56.8%)	
- Upper ureter	70 (9.9%)	
- Middle ureter	31 (4.4%)	
- Lower ureter	23 (3.3%)	
Left side	388 (54.9%)	
Right site	319 (45.1%)	
Male	343 (48.5%)	
Drainage		127 (18.0%)
- Pigtail stent		93 (13.2%)
- Nephrostomy		34 (4.8%)
Number of ESWL		
- One		503 (71.1%)
- Two		162 (22.9%)
- Three		40 (5.7%)
Antibiotics		219 (31.0%)
Small focus		697 (98.6%)

Table 2. Descriptive statistics for ESWL treatment when stones >2 cm are excluded. (n=707)

Variable	**Number (%)**
Outcome = Stone free < 4 mm (%)	330 (46.7)
Sex = Female (%)	364 (51.5)
Side = Left (%)	388 (54.9)
Location = Kidney (%)	579 (81.9)
Drainage type (%)	
None	580 (82.0)
Pigtail stent	93 (13.2)
Nephrostomy	34 (4.8)
Age (mean (SD))	61 (15)
HU (mean (SD))	939 (271)
Volume (median (IQR))	462 (252, 935)
SSD (mean (SD))	10.5 (2.5)

Table 3. Univariable analysis of factors that could affect SFR after ESWL (HU and volume are odds ratios/100 units, CI=confidence interval). (n=707)

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Sex Male	1.093	0.719	1.661	0.677
Side Right	1.241	0.815	1.889	0.315
Location Ureter	0.921	0.513	1.652	0.782
Pigtail stent	0.946	0.512	1.748	0.860
Nephrostomy	1.243	0.490	3.150	0.647
Age	0.947	0.932	0.963	**<0.001**
HU (100)	1.028	0.951	1.111	0.488
Volume (100)	0.940	0.910	0.972	**<0.001**
SSD	0.917	0.841	0.999	**0.047**
Max size	0.848	0.791	0.908	**<0.001**

Table 4. Multivariable analysis of factors that could affect SFR after ESWL, using Volume not max stone size (HU and volume are odds ratios/100 units). (n=707)

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Sex Male	1.253	0.78	2.014	0.352
Right side	1.322	0.815	2.142	0.258
Location Ureter	0.651	0.305	1.391	0.268
Pigtail stent	1.024	0.510	2.059	0.946
Nephrostomy	2.522	0.828	7.684	0.104
Age	0.944	0.928	0.961	**<0.001**
HU (100)	1.058	0.966	1.159	0.226
Volume (100)	0.940	0.908	0.973	**< 0.001**
SSD	0.974	0.874	1.085	0.634

Table 5. Lasso regression model for the most predictive factors for SFR after ESWL, using volume as the measurement of stone size (n=707)

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Age	0.947	0.932	0.963	< 0.001
Volume (100)	0.942	0.911	0.974	< 0.001

Table 6. Lasso regression model for the most predictive factors for SFR after ESWL, using max size (n=707)

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Age	0.954	0.939	0.969	< 0.001
Max size	0.851	0.791	0.916	< 0.001

Table 7. Multivariable analysis, subgroup of "First treatment" (n=503), of factors that could affect SFR after ESWL (HU and volume are odds ratios/100 units).

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Sex Male	1.191	0.675	2.102	0.546
Right side	0.943	0.532	1.672	0.841
Location ureter	0.697	0.276	1.761	0.446
Pigtail stent	0.853	0.319	2.280	0.751
Nephrostomy	1.222	0.264	5.651	0.798
Age	**0.942**	**0.922**	**0.961**	**< 0.001**
HU (100)	1.005	0.900	1.122	0.928
SSD	1.038	0.914	1.179	0.564
Max size	**0.828**	**0.752**	**0.912**	**< 0.001**

Table 8. Multivariable analysis, subgroup "Second treatment" (n=162), of factors that could affect SFR after ESWL (HU and volume are odds ratios/100 units). The small number of individuals in this subgroup led to very large confidence intervals.

Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Sex Male	1.991	0.698	5.682	0.198
Side, Right	1.517	0.549	4.191	0.421
Location Ureter	0.405	0.111	1.482	0.172
Pigtail stent	0.765	0.196	2.986	0.700
Nephrostomy	1.009	0.04	25.284	0.995
Age	0.954	0.916	0.993	**0.022**
HU (100)	0.965	0.800	1.164	0.711
SSD	1.047	0.826	1.328	0.703
Max size	0.963	0.822	1.129	0.643

Table 9. Pearson correlation analysis of variables that could be confounders (n=707).

Table 9	Age	**HU**	**Max size**	**SSD**
Age		-0.07	0.16	0.28
HU			0.23	-0.05
Max size				0.11
SSD				

Fig 1. Bland-Altman diagram presented interindividual measuring difference (randomly selected cases n=64)

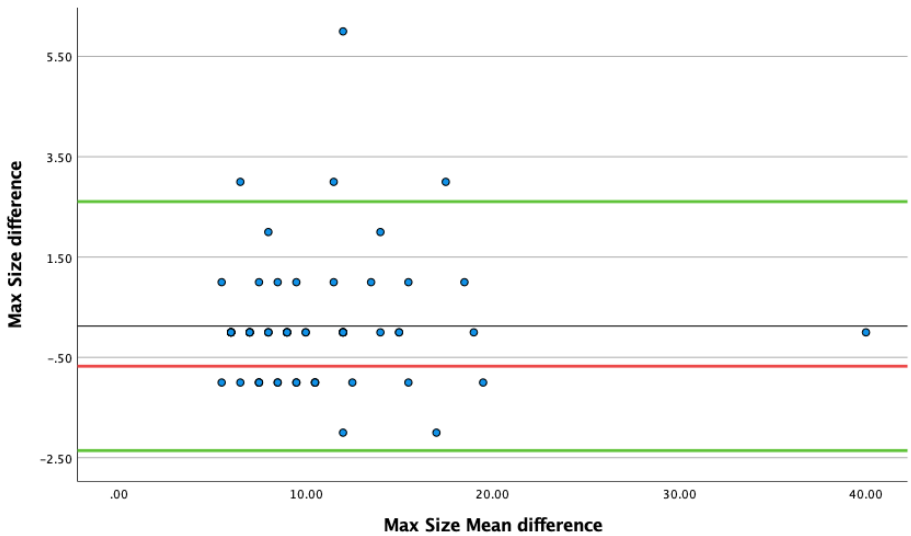


Fig 2. ROC analysis of the full model (blue) and a model including only age and maximum size (black). (n=707)

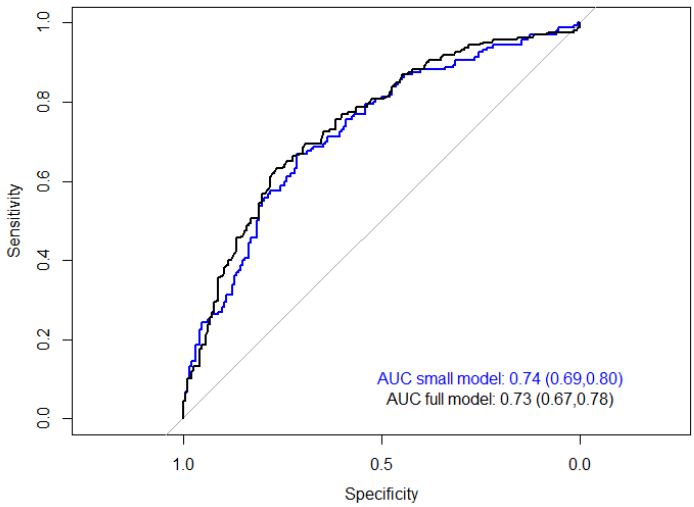


Fig 3. A visual diagram predicting SFR graphically age on y-axis and max stone size on x-axis.