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Recurrent renal colic in young people: Abdominal Munchausen syndrome - a diagnosis not to forget.
Tommaso Cai, Adolfo Pazzagli, Andrea Gavazzi, Riccardo Bartoletti
12th Course: Advances in Urological Oncology “Focus on Bladder Tumours”

The Course will be held under the auspices of:
- Italian Society of Urological Oncology (SIURO)
- University of Palermo • University of Bologna
- Faculty of Medicine of the Catholic University of the Sacred Heart of Rome
- Italian Ministry of Health
- Italian Ministry for Instruction, University and (Scientific) Research
- Sicilian Regional Government
- World Federation of Scientists

TOPICS

Pathobiology of invasive urothelial neoplasms: taxonomic aspects and classification; Morphological aspects; Revealing bladder cancer by prostatic technique; Molecular staging: are we ready to use it? Invasive cancer in the elderly; Bladder sparing: to spare or not to spare? Seminal sparing: to do or not to do? Laparoscopic cystectomy: myth or reality? Urinary diversion and quality of life; Morphopathology of urothelial cancer metastases; Pharmacogenomics: definition and techniques; Pharmacogenomic tests and bladder cancer; T and M categories: can the imaging tell us more? Neoadjuvant and adjuvant therapy in locally advanced disease; Chemotherapy in advanced disease; New drugs; Radical cystectomy: early or late? Urothelial tumours of the upper urinary tract: are they a different disease? Clinical diagnosis of the upper urinary tract neoplasms; Cytogenetic and histological diagnosis; Surgical versus endourological approach to upper urinary tract neoplasms; Non urothelial bladder cancers; Laparoscopic nephroureterectomy; Extensive lymphadenectomy for upper urinary tract tumours; Advanced urothelial neoplasia: which role for radio-chemotherapy? Cancer and bone: still a chance! Every afternoon role playing on daily issues session will take place.

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Pier Francesco Bassi, Roma • Italy
Francesco Boccardo, Genova • Italy
Enrico Bolli, Orbasco (TO) • Italy
Sergio Braccard, Perugia • Italy
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Vincenzo Ficarra, Verona • Italy
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PURPOSE OF THE COURSE

The purpose of the Course is to provide state-of-the-art knowledge and future perspectives on basic and translational research, detection techniques and advanced therapeutic strategies of bladder tumours in a multidisciplinary approach. Scientific sessions will include interactive discussions between the faculty and the participants. International experts in research and treatment of bladder tumours will share their views and experience with the audience. This Course is the second of a series of courses held under the aegis of the Italian Society of Urological Oncology. It is hoped to organise such courses on alternate years.

GENERAL INFORMATION

Accreditation for Continuing Medical Education (CME) by the European Board of Urology (EBU) and by the Italian Ministry of Health (ECMI: Educazione Continua in Medicina) will be applied.

The registration fee for participants – € 2,000.00 plus VAT to be paid within January 31st 2008 to the Organising Secretariat – is inclusive of: scientific sessions, transfer from airport (Palermo or Trapani) to Erice and viceversa, lodging on full board basis and social events.

Emce, Sicily • Italy • April 7-11, 2008
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INTRODUCTION
Renal colic is a common emergency department (ED) presentation and trend data indicate that the volume of visits for renal colic is still increasing during the last years (1) accordingly with the reported increase of the prevalence of calcium stones (2). In the United States (3) a recent survey of more than 25,000 ED visits showed a total of 259 records with a primary diagnosis of renal calculus or colic representing an approximate rate of 1%. Three patients were hospitalised for immediate urinary diversion due to anuria or sepsis. Fifty-three patients recovered without performing any pharmacological treatment. Analgesic treatment (mainly NSAID) was offered to 439 patients. After a 6 hour period 36 patients were admitted to the hospital owing to persistent pain. Pain was reduced in 403 patients (91.8%) who were offered outpatient renal ultrasound within 48 hours. Twenty-five patients (6.2%) required deferred hospitalisation. Follow up with renal ultrasound was obtained in 213.

Conclusion: Renal colics accounted for 0.9% of ambulatory care visits to our emergency departments with an annual rate of 0.158 visits per 100 in the general population. NSAIDs were efficacious in the management of colic. Diagnostic work up was able to demonstrate the presence of a stone in 56% of the subjects presenting with renal colic whereas alternative diagnoses were demonstrated in 12%.

KEY WORDS: Colic; Epidemiology; Management; Pain; Prevalence; Sonography; Urinary calculus.

Summary
Background/Aims: To assess the incidence of renal colic and the results of emergency management.
Methods: During a 12 month period data of patients with symptoms of renal colic were collected.
Results: A total of 495 visits were registered. The M/F was 2.19. Mean age was higher in males (45.5±13.0 vs 42.5±15.5 years, P = 0.025). Three patients were hospitalised for immediate urinary diversion due to anuria or sepsis. Fifty-three patients recovered without performing any pharmacological treatment. Analgesic treatment (mainly NSAID) was offered to 439 patients. After a 6 hour period 36 patients were admitted to the hospital owing to persistent pain. Pain was reduced in 403 patients (91.8%) who were offered outpatient renal ultrasound within 48 hours. Twenty-five patients (6.2%) required deferred hospitalisation. Follow up with renal ultrasound was obtained in 213.
Conclusion: Renal colics accounted for 0.9% of ambulatory care visits to our emergency departments with an annual rate of 0.158 visits per 100 in the general population. NSAIDs were efficacious in the management of colic. Diagnostic work up was able to demonstrate the presence of a stone in 56% of the subjects presenting with renal colic whereas alternative diagnoses were demonstrated in 12%.

INTRODUCTION
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MATERIALS AND METHODS
From July 2004 to June 2005 data of patients who presented with symptoms of renal colic to the emergency departments of the two hospital of our district were
prospectively collected by means of a predisposed data form. All the patients were managed according to our internal guideline. At admission previous medical history was collected and accurate physical examination was obtained for all the patients. A blood sample was taken from all patients and was analysed for blood count, electrolytes, creatinine and amylase and an urine sample was collected for dipstick examination. Patients with colic associated to acute renal insufficiency, sepsis and solitary kidney were immediately hospitalised. If necessary, they underwent immediate urinary diversion. Other patients were asked to score their pain by means of a visual analogue score. Analgesic parenteral treatment was offered to the patients with significant pain score. The first option were non steroidal antiinflammatory drugs (NSAIDs) The protocol included as possible preferred alternatives diclofenac (75 mg) or kotorolac (30 mg). Opiates were administered to patients with known hypersensitivity or intolerance to NSAIDs. A second medication was prescribed after 3 hours to patients with incomplete or no response to first medication. Generally opiates were offered to patients non responding to previous NSAID administration. After 6 hours of observation pain was again scored. Patients with persistent incoercible pain were admitted to the hospital. Renal ultrasound and intravenous pyelography (IVP) or helical computerised tomography (CT) were performed and patients with ureteral stones underwent appropriate surgical or medical treatment. Patients with complete or significantly reduction of pain were discharged and offered conservative measures and outpatient renal ultrasound and urologic visit within 48 hours in the hospital. At follow up visit all relevant radiological, biochemical and serological investigations were noted.

**RESULTS**

Over 1-year study period, 495 patients presented to the ED with suspected renal colic. Demographics are presented descriptively in Table 1. The majority of patients were males with a male to female ratio 2.19 to 1. ED visits for renal colic were more frequent in September and December (Figure 1). Mean age was significantly higher in males than in females (45.5±13.0 vs 42.5±15.5 years, P = 0.025). In particular mean age was higher in males presenting during Summer months with respect to females presenting in the same period (47.2±13.2 vs 40.4±15.9 years, P=0.023), whereas no significantly difference was observed during the rest of the year.

Three patients were immediately hospitalised for urinary diversion, respectively for anuria associated to solitary kidney, acute renal insufficiency due to bilateral ureteral stones and sepsis. Fifty-three patients recovered without performing any pharmacological treatment. Analgesic parenteral treatment was offered to the remaining 439 patients: NSAIDs in 418, opiates in 15 and other drugs in 6 (Table 2). The most commonly used NSAID was diclofenac. In 44 patients with persisting pain after the first NSAID administration, a second dose of NSAID (8 pts) or opiate (30 pts) or tramadol (6 pts) was administered. At the end of the 6 hour observation other 36 patients were admitted to the hospital owing to persistent incoercible pain. Pain was significantly reduced in 403 patients (91.8%) who were offered outpatient renal ultrasound and urologic visit within 48 hours. Deferred hospitalisation was required in 25 (6.2%) of them who presented with recurrent flank pain within 48 hours from the discharge. During hospitalisation renal ultrasound and/or IVP (or helical CT) were performed demonstrating the presence of ureteral stones in 37 out of 64 hospitalised patients (57.8%). Out of them, 3 underwent immediate urinary diversion, 10 extracorporeal lithotripsy, 6 endoscopic treatment, 4 ureteral manipulation with medical treatment and 14 medical treatment alone. In two cases stones were sponta-

<table>
<thead>
<tr>
<th>Season</th>
<th>N° patients</th>
<th>M</th>
<th>F</th>
<th>M/F</th>
<th>Age</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring</td>
<td>96</td>
<td>64</td>
<td>32</td>
<td>2.00</td>
<td>44.2±14.0</td>
<td>45.6±14.0</td>
<td>41.5±13.9</td>
</tr>
<tr>
<td>Summer</td>
<td>111</td>
<td>74</td>
<td>37</td>
<td>2.00</td>
<td>44.9±14.5</td>
<td>47.2±13.2</td>
<td>40.4±15.9*</td>
</tr>
<tr>
<td>Autumn</td>
<td>151</td>
<td>110</td>
<td>41</td>
<td>2.68</td>
<td>44.8±13.6</td>
<td>45.1±12.7</td>
<td>44.0±15.9</td>
</tr>
<tr>
<td>Winter</td>
<td>137</td>
<td>92</td>
<td>45</td>
<td>2.04</td>
<td>44.3±13.6</td>
<td>44.8±12.4</td>
<td>43.5±16.0</td>
</tr>
<tr>
<td>Total</td>
<td>495</td>
<td>340</td>
<td>155</td>
<td>2.19</td>
<td>44.5±13.8</td>
<td>45.5±13.0</td>
<td>42.5±15.5**</td>
</tr>
</tbody>
</table>

* P = 0.023 (M vs F); ** P = 0.025 (M vs F)

**Table 1.**

Demographics of patients with renal colic by season of presentation.

**Figure 1.**

Patients with renal colic by sex and month of presentation.
neously passed out after conservative treatment (Table 3). Non stone urological and non urological diseases were diagnosed in 11 patients (18%). Diagnoses were in details: ureteropelvic junction (UPJ) stenosis in 3 patients, urothelial cancer of the renal pelvis, pyelonephritis, neurological syndromes (radiculitis, peripheral post traumatic neuritis, herpes zoster) in 6 patients. Out of the group of non-hospitalised patients, follow up with renal ultrasound was obtained in 213. Previous passage or presence of an urinary stone were demonstrated in 120 patients (56.3 %) (Table 4). In other 22 cases (10.3%) we were able to demonstrate alternative diagnoses: pyelonephritis (5 pts), urinoma, partial renal infarction, renal hypoplasia, pelvic kidney, polycystic kidney, bladder tumour, benign prostatic hyperplasia (BPH), epididymitis, radiculitis (3 pts), dorsal myalgia (2 pts), ovarian cyst (2 pts), endo-triostis, chest pain. Diagnostic work up was negative in 16 (25%) of hospitalised and in 71 (33.3%) of non hospitalised patients.

**DISCUSSION**

Renal colics accounted for approximately 0.9 % of all ambulatory care visits to emergency departments of our hospital (55,000 per year). According to these data the annual rate of visits for renal colic in our district (313,000 inhabitants) can be estimated in 0.158 visits per 100 persons. In fact almost all emergency visits are centralised in two hospitals being our district a geographically isolated area with most of the population living in the valleys surroundings the eastern side of the lake of Como. The annual incidence of renal colic is relevant and it could be easily explained by the still increasing incidence of the renal stone disease in Italy, as in most of the Western countries (1). On the other hand rates obtained by our survey are quite similar to rates previously reported in US hospitals (3, 4). We were not able to confirm that renal colics are more likely in warmer than in colder months. This could be explained by the fact that the greater part of the territory of our district is mountainous with relatively cold climate also during Summer period. In fact seasonal trends in the incidence of nephrolithiasis have been previously recorded in regions with temperate climates (5) while this trend was not confirmed in Scandinavia, where there are no high temperatures in the Summer period (6). On the contrary the higher age of male patients during Summer months could be related to an increased risk for uric acid precipitation in older men due to dehydration.

<p>| Table 2. |</p>
<table>
<thead>
<tr>
<th>Results of pharmacological treatment of renal colic.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N° patients</strong></td>
</tr>
<tr>
<td>Analgesic treatment</td>
</tr>
<tr>
<td>1st medication</td>
</tr>
<tr>
<td>NSAIDs (total)</td>
</tr>
<tr>
<td>Diclofenac</td>
</tr>
<tr>
<td>Ketorolac</td>
</tr>
<tr>
<td>Ketoprofene</td>
</tr>
<tr>
<td>Opiates (total)</td>
</tr>
<tr>
<td>Morphin</td>
</tr>
<tr>
<td>Metadon</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>1st+2nd medication</td>
</tr>
<tr>
<td>NSAIDs+NSAIDs</td>
</tr>
<tr>
<td>NSAIDs+tramadol</td>
</tr>
<tr>
<td>NSAIDs+opiates</td>
</tr>
</tbody>
</table>

<p>| Table 3. |</p>
<table>
<thead>
<tr>
<th>Treatment of hospitalised patients with urinary stones.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate hospitalisation</strong></td>
</tr>
<tr>
<td>Urinary diversion</td>
</tr>
<tr>
<td>SWL</td>
</tr>
<tr>
<td>Endoscopic treatment</td>
</tr>
<tr>
<td>Medical treatment with ureteral manipulation</td>
</tr>
<tr>
<td>Medical treatment alone</td>
</tr>
<tr>
<td>Spontaneous passage</td>
</tr>
</tbody>
</table>

<p>| Table IV. |</p>
<table>
<thead>
<tr>
<th>Results of renal ultrasound and urologic visit in 213 non-hospitalised patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary tract US</strong></td>
</tr>
<tr>
<td>Spontaneous stone passage</td>
</tr>
<tr>
<td>Calyceal stones or microliths without hydronephrosis</td>
</tr>
<tr>
<td>Mild hydronephrosis with/without stone demonstration</td>
</tr>
<tr>
<td>Non passable stones – severe hydronephrosis</td>
</tr>
<tr>
<td>Alternative diagnoses</td>
</tr>
<tr>
<td>Negative</td>
</tr>
</tbody>
</table>
Finally the explanation of the bout of renal colics observed in December could be related to the possible risk associated with the consumption of a lithogenic diet during the period of Christmas holidays (alcohol, proteins) although this contrasts with the observation of no significant decrease of the frequency of admissions for renal colic observed in Pakistan during the fasting period of Ramadan (7). The rate of hospitalisation was about 13%, a relatively high figure considering that in the United States fewer than 10% patients presenting with renal colic are admitted to hospital (3). This rate is even more disappointing if we consider that in about 25% of the admitted patients the diagnostic work up was not able to demonstrate the presence of a definite disease. According to our protocol the option to admit the patient was exclusively based on the response of pain to pharmacological treatment and of the laboratory tests deferring renal ultrasound to the follow up visit. Routine use of imaging would probably reduce the admission rate by demonstrating the absence of ureteral stones or urinary dilatation in some doubtful cases, but the burden of diagnostic work up would be made heavier especially during night time. NSAIDs confirmed to be highly efficacious in the treatment of pain related to renal colic, in particular diclofenac achieved the highest rate of pain remission. The efficacy of opiates was only slightly lower, whereas other drugs proved to be less useful (tramadol, anticolinergics).

The relatively low diagnostic rate of our radiological work up could be related to the fact that unenhanced computed tomography was not routinely used for diagnosis of renal colic. During the past decade, unenhanced computed tomography has become the standard of reference in the detection of urinary calculi owing to its high sensitivity (>95%) and specificity (>98%) in this setting (8).

In our institution the switch from urography to unenhanced CT and CT urography for the management of patients with renal colic was still not done owing to the inadequacy to sustain a so large burden of supplemental work. On the other hand the combination of plain film and ultrasound remains an alternative to unenhanced CT with a lower sensitivity but a lower radiation dose that still has a good practical value. Using helical CT findings or passage of a stone as the gold standard, plain radiography showed a sensitivity of 69% and specificity of 82% (9). Renal colic is still a frequent indication for IVU but when performed due to renal colic it was able to found a calculus in the upper urinary tract in only 27% (11). A definite vantage of unenhanced CT examination is its capability to reveal unsuspected findings unrelated to stone disease. In fact in patients with acute flank pain studied by unenhanced computed tomography the incidence of incidental additional or alternative diagnosis was 12-39% (11, 12). In conclusion we confirm that renal colics account for a significant rate of all ambulatory care visits to the emergency department of an European district.

NSAIDs were highly efficacious in the acute management of colic, but a significant number of patients relapsed requiring hospital admission in the subsequent 48 hours owing to the persistence of acute flank pain. A maintenance treatment was not included in our schedule, whereas the use of alpha-blockers or other drugs after discharge could be an option for reducing the number of patients with relapsing pain. Diagnostic work up was able to demonstrate the presence of a stone in the urinary tract in up to 56% of the subjects presenting with renal colic and alternative diagnoses were made in another 12%, but in a further 30% of cases the pain remained unexplained. Passage of “gravel” is a common explanation for these cases that often remain asymptomatic in the follow up. Diagnostic efficacy could be improved by the adoption of enhanced CT for all the cases presenting with renal colic but at the moment this option still represents an excessive cost for our imaging emergency unit especially during night time.

References

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Infections and urolithiasis: Current clinical evidence in prophylaxis and antibiotic therapy.

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Urinary tract infections and urosepsis are complications which can precede or follow a kidney stone treatment. Often the stones themselves are the source of infection, whether they are infection stones or not. Systemic infections are difficult to foresee, and neither a pre-operative negative urine culture nor an antibiotic prophylaxis avoid infectious complications for certain. The primary predictive risk factors of urosepsis are: patient conditions, urinary tract infection or a history of recurrent infections, characteristics of the stone, and anatomy of the urinary tract. Infection stones are still a matter of debate, concerning both the aetiology of the disease and its treatment. Positive cultures are not only found with struvite stones, but also with apatite and calcium oxalate stones. Currently, a long-term antibiotic therapy is advised in patients affected by infection stones. Antibiotic therapy should prevent not only septic complications but also recurrence or re-growth of stones after treatment. Different antibiotic modalities are recommended, sometimes together with urease inhibitors. Mid-stream urine culture is the easiest available pre-treatment parameter notwithstanding its poor predictive value. In case of suspected or proven urinary infection, an appropriate antibiotic therapy should always be administered prior to surgical procedure. There is, however, controversy regarding the antibiotic use, its role, expediency, and duration of prophylaxis in relation to the various surgical procedures, and the way infectious complications are considered and classified. When antibiotic prophylaxis is considered, its duration should be clearly established prior to surgery; duration may vary depending on the type of surgery or the type of antibiotic. Furthermore, prophylaxis should be administered only for a limited amount of time. In infection stones, in immuno-compromised patients or in patients with anatomical anomalies or diabetes, the risk of post-treatment infection and sepsis is higher. Hence there is agreement on the need for prophylaxis and antibiotic therapy. The most recent literature has shown excellent results with fluoroquinolones both in prophylaxis and therapy, concerning post-operative infection control after percutaneous as well as ureteroscopic removal of stones. No agreement has yet been reached on antibiotic prophylaxis modalities prior to percutaneous or ureteroscopic removal and its usefulness for SWL.

KEY WORDS: Urolithiasis, Infection, Antibiotic prophylaxis, Antibiotic therapy.
PATHEGENESIS OF INFECTION STONES

Infection stones (struvite stones and/or carbonate apatite) account for 10-30% of urinary stones. Formation of infection stones depends on urea hydrolyzing in the presence of urease by urease-producing bacteria (Table 1).

Ammonia and carbon dioxide are transformed in ammonium bicarbonate, which subsequently binds with available urinary cations producing magnesium ammonium phosphate (struvite) and carbonate apatite (Figure 1). However, the study by Hugosson et al. (4) showed the presence of urease-producing organisms in only 48% of struvite stones, while 32% of calcium oxalate stones were infected. It may therefore be inferred that an infection from urease-producing organisms is not always present in infected struvite stones; furthermore, positive cultures can be obtained not only from struvite stones, but also from calcium oxalate stones (4,5). Nanobacteria have also been suggested to cause stone disease and be pathogenic for urosepsis following kidney stone treatment. Nanobacteria are micro-organisms that are 10-100 times smaller than normal bacteria; they may be involved in the formation of calcium phosphate crystals, thus creating nidi for the formation of the stone. The risk of sepsis would therefore be correlated with the release of these micro-organisms from the stone during treatment (6). Endotoxins are another factor supposed to be involved in the pathogenesis of urinary infection from kidney stones. High levels of endotoxins are found both in infection stones (struvite and carbonate apatite stones), and in non infection stones. High concentrations of these lipopolysaccharides are thought to be released in the systemic circulation during stone treatment, inducing an inflammatory response. The process is apparently amplified in the presence of obstructive uropathy, due to the increased permeability of the blood and lymphatic vessels of the renal pelvis (7).

The primary predictive risk factors of urosepsis are the following: patient conditions such as immunodepression and a deteriorated performance status, a urinary infection in progress or a history of recurrent infections, characteristics of the stone, anatomy of the urinary tract (1). Therefore, besides accurately evaluating the patient, it is advisable to perform a urine culture prior to treatment, although a negative urine culture does not totally rule out the possibility of even severe septic complications (8). Agashi et al. showed that in staghorn stones urine culture was positive only in about 20% of patients, but stone culture was positive in 50% (9). According to Mariappan in case of obstructive stones, bladder urine culture was negative, whereas stone culture was positive in 25% of cases and the culture of the upper urinary tract urine was positive in 66% of cases. The size of the stone appears to be correlated to the presence of bacteria in the stone itself, as a positive culture of the stone was shown in 21.3% of stones < 20 mm and in 43.6% of those > 20 mm (5). Renal pelvic dilatation also appears to be correlated with an infection of the pelvic urine (5).

Intraoperative samples can therefore be used as guides for antimicrobial therapy. Cultures of stone fragments and upper urinary tract urine are more indicative than mid-stream urine culture alone. Despite the fact that upper urinary tract urine or stone bacteriology is available only after treatment, it can be useful in infections resistant to the normally employed empirical broad-spectrum therapies. There is, however, not always a correspondence between isolated micro-organisms from bladder and renal pelvis urine and stone cultures. In the study by Gault, the same micro-organism was isolated from the stone and from mid-stream urine in only 38% of cases (10).

Mariappan (11) performed pre-operatively cultures from midstream urine, from pelvic urine and from stone fragments. Whereas 34% of stones were infected, 59% of pelvic urine samples were found to be infected and only 29% of pre-treatment urine cultures were positive, with
a growth of the same micro-organism in only 23-25% of cases. Mid-stream urine culture therefore has been found to have scarce predictive value for an infection of the upper urinary tract. Patients with infected stones and upper urinary tract have a 4 times greater risk of developing urosepsis (5).

**TREATMENT OF INFECTION STONES AND STONES WITH INFECTION**

In agreement with the recent American Urological Association (AUA) guidelines, the goal of treating classic infection stones must be complete clearance of the stones. Residual stones cause persistent infection and rapid stone re-growth (in 61% after surgical therapy (12) and in 65-78% after SWL (13, 14). Antibiotics eliminate bacteriuria, but the persisting stones or residual fragments compromises the possibility of eradicating the infection. Persisting urinary tract infection increases the risk of stone recurrence. In patients with infected staghorn stones treated by Meretyk, stone recurred in 33.3% of cases post-SWL and in 22% after PCNL (14). Currently, a long-term antibiotic therapy is advised in patients with infection stones. Antibiotic therapy can reduce the bacterial load significantly, although urine does not become sterile. Besides contrasting septic risks, antibiotics prevent recurrence or re-growth of stones after treatment. Acetohydroxamic acid has been used in association with antibiotic therapy in patients with infection stones who had contraindications to surgery (15). In the literature, different types of pre-treatment targeted antibiotic therapy are found, sometimes together with urease inhibitors (Table 2).

Anti-nanobacterial therapy (tetracyclines administered with nutraceuticals and EDTA) has been suggested for cases in which nanobacteria are suspected (16). Antibiotic therapy should be continued while complete stone removal is aimed at by all possible treatment modalities, including PCNL, SWL, and open surgery (Table 3).

**EAU GUIDELINES FOR ANTIBIOTIC PROPHYLAXIS OF URINARY STONE**

The guidelines of the European Association of Urology for the management of urinary and male genital tract infections strongly recommended peri-operative prophylaxis for the prevention of infection related to surgical procedures (17). However it should be pointed out that antibiotic prophylaxis is only one component of the infection prevention management and that it cannot compensate for poor hygiene and operative technique. Peri-operative antibiotic prophylaxis is intended to prevent symptomatic and/or febrile urinary tract infections, acute pyelonephritis, urosepsis, acute prostatitis, epididymitis and severe wound infections. The indication depends on the type of procedure and the individual risk for infection including the presence of urinary stones. Antibiotic prophylaxis could be debatable in patients with sterile urine and without risk factors for infection in absence of intraoperative complications. In order to avoid antibiotic prophylaxis a negative preoperative urine culture is mandatory. The correct timing of antibiotic administration is crucial. Parenteral administration should be given at induction of anesthesia whereas oral drugs should be given 1-2 hours before the procedure. Longer procedures (> 2.5-3 hours) require additional administration according to the pharmacokinetics of the antibiotic. Prophylaxis should not be extended beyond 24 hours after the procedure.

**Table 2.**

*Treatment for infection stones.*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streem, J Urol, 1997</td>
<td></td>
<td>1 or 2 weeks of pre-operative targeted antibiotic therapy + broad-spectrum IV therapy intra- and post-operatively</td>
</tr>
<tr>
<td>Wang, Urol Clin, 1997</td>
<td></td>
<td>Targeted antibiotic therapy + urease inhibitors as completion of the PCNL + SWL treatment</td>
</tr>
<tr>
<td>Margel, Adult Urology, 2006</td>
<td></td>
<td>2 weeks of targeted antibiotic therapy prior to treatment (referring to the most recent positive urine culture)</td>
</tr>
<tr>
<td>Sharifi, Surgical Inf, 2006</td>
<td></td>
<td>1-2 days of antibiotic prophylaxis prior to treatment</td>
</tr>
</tbody>
</table>

**Table 3.**

*Treatment of complete or partial staghorn stones (EAU Guidelines, 2007).*

<table>
<thead>
<tr>
<th>Type of stone</th>
<th>Procedure</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection stones and stones with infection</td>
<td>1. Antibiotics + PCNL</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2. Antibiotics + PCNL+ ESWL</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>3. Antibiotics + ESWL + PCNL</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>4. Antibiotics + ESWL + local chemolysis</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>5. Antibiotics + open surgery</td>
<td></td>
</tr>
</tbody>
</table>
The **EAU guidelines** suggest antibiotic prophylaxis for extracorporeal lithotripsy and ureteroscopy of uncomplicated stones of the distal ureter only in risk patients (e.g. when an ureteral stent or a nephrostomy is present). Perioperative antibiotics should be routinely administered for ureteroscopy of stones in the proximal ureter or impacted stones, for percutaneous nephrolithotomy or open stone surgery (Table 4).

### Percutaneous Lithotripsy (PCNL)

Although turbid urine obtained by renal puncture does not always predict infection, it is advisable to leave a nephrostomy in place and to postpone the percutaneous treatment of stones until the urine is found to be sterile or infection has been treated effectively. Several Authors have shown an increased septic risk (including fatal risk) following instrumentation of an infected caliceal system (5). The incidence of urosepsis does not increase with the frequency of punctures of the caliceal-pelvic cavities during PCNL (18). There is also no correlation between the duration of the procedure and the occurrence of infectious complications (19).

In patients with negative pre-operative urine culture without antibiotic prophylaxis, Charton et al. observed urinary tract infection in 35% of patients (20). Several authors have shown prophylaxis followed by antibiotic therapy markedly reduces the incidence of urinary tract infections and post-operative hyperpyrexia (19, 21).

If there is pre-operative urinary tract infection present, a targeted antibiotic therapy should be administered until the urine culture is negative, or a cycle of broad-spectrum antibiotic should be administered prior to surgery (22).

Recently, the use of fluoroquinolones has been proposed. Mariappan (23) studied ciprofloxacin prophylaxis administered one week prior to surgery on patients with staghorn stones (> 20 mm) and/or pyelocaliceal dilatation. The results were compared with those of a group of patients with the same characteristics but without prophylaxis (control group). In the patients who underwent prophylaxis (ciprofloxacin 250 mg x 2/day orally), a 3-fold lower risk of upper urinary tract infections and systemic inflammatory response syndrome (SIRS) was observed, and considerably less positive pelvic and stone cultures were found. In these patients, oral administration of ciprofloxacin therefore reduced the risk of urosepsis significantly. Another study proposed ofloxacin with different types of administration (oral and intravenous), but no significant differences were observed in the prevention of infectious complications. Results were similar to those obtained with ciprofloxacin (24).

### Ureterolitholapaxy (ULL)

During this procedure, the hydrostatic pressure generated by the irrigation fluid causes migration of bacteria and endotoxins into the systemic circulation. This process is apparently amplified in the presence of urinary obstruction, because of the greater permeability of the blood and lymphatic vessels of the renal pelvis. Therefore, the incidence of systemic infections can be reduced with systems of low-pressure irrigation or using a flexible ureteroscope with a ureteral access sheath (25).

Of all fluoroquinolones with prevalent renal excretion, full-dose (500 mg/day) of levofloxacin plays a primary role in the treatment of urinary tract infections due to the high concentration achieved in the urinary tract (higher than 300 mcg/ml after 6 hours) (26).

Knopf compared two groups of patients who underwent endoscopic removal of ureteral stones: the first group underwent prophylaxis with one-shot levofloxacin 250 mg orally, one hour prior to treatment, while the second had no prophylaxis. No acute infectious complications were observed in the patients who received levofloxacin prophylaxis (27).
was observed in either group, but there was a relevant reduction in bacteriuria in patients with prophylaxis. Levofloxacin therefore successfully reduced possible postsurgical infectious complications (27).

Tenke evaluated patients with ureteral stents and/or percutaneous nephrostomy for acute urinary tract infection secondary to ureteral obstruction. Patients were treated with levofloxacin 500 mg by continuous or intermittent therapy (before endoscopic treatment). Apparently there were no significant differences between the two groups as to clinical complications. Moreover the concentration of levofloxacin on the surface of the stent or within the biofilm was higher than the MICs of the main uropathogens (28). Also there were no differences between a prophylaxis with levofloxacin given orally or intravenously (29).

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (SWL)
Renal and vascular trauma caused by SWL treatment can lead to the passage of bacteria from the urine into the systemic circulation. Skolarikos et al. found post-SWL bacteriuria in 7-23% of patients, bacteraemia in 14% with evolution towards urosepsis in less than 1% of cases (in infection stones this percentage rose to 2.7%) (30). The risk of sepsis is higher in patients with positive pre-treatment urine culture and/or urinary obstruction (31). The role of antibiotic prophylaxis for SWL is still controversial. Despite some Authors support routine antibiotic prophylaxis (32), the most recent studies did not show a better prevention of infection in the absence of pre-existing urinary tract infections or infected stones. There is, however, agreement on routine antimicrobial prophylaxis in infection stones with or without positive urine culture, in patients with history of recurrent urinary tract infections, and in patients with stents or nephrostomies (30, 31, 33-35) (Table 5).

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>Prophylaxis/ therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charton, 1986</td>
<td>PCNL</td>
<td>No prophylaxis</td>
<td>35% UTI</td>
</tr>
<tr>
<td>Cadeddu, 1998</td>
<td>PCNL</td>
<td>Prophylaxis + Therapy (Gentamicin + Ampicillin or Cephalosporins)</td>
<td>16% fever (&gt;38°C)</td>
</tr>
<tr>
<td>Margel, 2006</td>
<td>PCNL</td>
<td>Prophylaxis (Cephalosporins II gen 1g one shot)</td>
<td>22% SIRS</td>
</tr>
<tr>
<td>Aghdas, 2006</td>
<td>PCNL</td>
<td>No prophylaxis</td>
<td>25.8% fever (&gt;38°C)</td>
</tr>
<tr>
<td>Mariappan, 2006</td>
<td>PCNL</td>
<td>Prophylaxis (Ciprofloxacin 500mg x2/day orally for 1 week)</td>
<td>3% SIRS</td>
</tr>
<tr>
<td>Dogan, 2002</td>
<td>PCNL</td>
<td>Prophylaxis (Ofloxacin 200mg IV one shot)</td>
<td>20% fever</td>
</tr>
<tr>
<td>Dogan, 2002</td>
<td>PCNL</td>
<td>Therapy (Ofloxacin 400mg/day orally)</td>
<td>21% fever</td>
</tr>
<tr>
<td>Knopf, 2003</td>
<td>ULL</td>
<td>Prophylaxis (Levofloxacin 250mg one shot)</td>
<td>1.8% bacteriuria</td>
</tr>
<tr>
<td>Knopf, 2003</td>
<td>ULL</td>
<td>No prophylaxis</td>
<td>12.5% bacteriuria</td>
</tr>
<tr>
<td>Tenke, 2006</td>
<td>ULL</td>
<td>Continuous therapy (Levofloxacin 500mgx2/day for 18-21 days)</td>
<td>12% UTI</td>
</tr>
<tr>
<td>Tenke, 2006</td>
<td>ULL</td>
<td>Intermittent therapy (Levofloxacin 500mgx2/day for 7+3 days)</td>
<td>12% UTI</td>
</tr>
<tr>
<td>Costantino, 2005</td>
<td>ULL</td>
<td>Prophylaxis + Therapy (Levofloxacin 500mg 4h pre-operatively + Levofloxacin 500mg for 5 days)</td>
<td>14% UTI</td>
</tr>
<tr>
<td>Dincel, 1998</td>
<td>SWL</td>
<td>Prophylaxis</td>
<td>2.17% UTI</td>
</tr>
<tr>
<td>Petterson, 1989</td>
<td>SWL</td>
<td>No prophylaxis (urine culture negative prior to treatment)</td>
<td>8.15% UTI</td>
</tr>
<tr>
<td>Bierkens, 1997</td>
<td>SWL</td>
<td>No prophylaxis (urine culture negative prior to treatment)</td>
<td>4.12% UTI</td>
</tr>
<tr>
<td>Zanetti, 1992</td>
<td>SWL</td>
<td>No prophylaxis (urine culture negative prior to treatment)</td>
<td>7.3% UTI</td>
</tr>
</tbody>
</table>

Table 5.
Clinical evidence on antibiotic prophylaxis/treatment before and after different procedures for stone removal.
for Disease Control (CDC). The combined analysis of PEP study and PEAP study showed a cumulative prevalence of NAUTIs of 11%. Several risk factors were identified such as presence of urinary catheters and duration of catheterization, history of previous urinary tract infections (UTI) and hospitalisation in the previous 6 months (Table 6 and 7). In particular NAUTIs were associated to urinary stones in 20%.

**THE ROLE OF BIOFILMS IN ANTIBIOTIC TREATMENT AND INFECTED STONES**

The pathogenic nature of bacteria associated with urinary stones can be enhanced by their ability to form surface-associated, protected communities known as “biofilms”. Biofilms are important as environmental reservoirs for pathogens. Biofilm may provide organisms survival advantages in natural environments and increase their virulence. Bacteria in biofilm communities display significantly greater resistance to traditional antimicrobial therapies.

In fact one of the distinguishing characteristics of biofilms is the production of an exopolysaccharide matrix that prevents access of antibiotics to the bacterial cells embedded in the community. Biofilm infection may increase the minimal inhibitory concentrations (MIC) of the antibacterials at the site of infection by several hundred folds. Assessment of antibacterial pharmacodynamic properties in such situations should take into account not only the MIC as determined in vitro, but also the actual urinary bactericidal activity of the antibacterial substance (37).

Employing in vitro and in vivo models of catheter-associated infection, Goto et al. (38, 39) investigated biofilm formation of *Pseudomonas aeruginosa* in artificial urine and bactericidal activity of several classes of antimicrobial agents. Fluoroquinolones showed the most potent bactericidal activity against the *P. aeruginosa* biofilm generated in urines. In particular ciprofloxacin as well as levofloxacin eradicated biofilm bacteria completely in 24 hours at a concentration 32 times the MBC. Furthermore the combined treatment with fosfomycin and fluoroquinolones with high antipseudomonal activity has effectively eradicated sessile cells of *P. aeruginosa* in the biofilm and may be beneficial against biofilm associated infectious diseases (40).

Urinary tract infections complicated by urinary stones should empirically be treated by compounds, which exhibit sufficient urinary bactericidal activity against Gram-negative as well as Gram-positive uropathogens. In particular ciprofloxacin (500 mg twice daily) and levofloxacin (500 mg once daily) may be suitable regimens in the treatment of severe complicated UTI.

In urinary tract infections caused by less susceptible uropathogens, such as *Pseudomonas aeruginosa*, an even higher dose could be administered, e.g. ciprofloxacin 750 mg twice daily and levofloxacin 500 mg twice daily.

**CONCLUSION**

Mid-stream urine culture, notwithstanding its scarce predictive value, is the most simple pre-treatment parameter available. Despite the fact that upper urinary tract urine or stone bacteriology is available only after treatment, it can be useful in infections resistant to the normally employed empirical broad-spectrum therapies. Mortality from severe Gram-negative sepsis reaches 29-50%. Therefore, when urosepsis is suspected an aggressive approach is always called for, including a broad-spectrum high-dose antibiotic therapy, total parenteral nutrition, and if necessary the aid of intensive therapy. In case of suspected or proven urinary infection, an appropriate antibiotic therapy should be always administered prior to treatment.

Antibiotic therapy is still controversial in regard to its role, expediency, and duration of prophylaxis in various surgical procedures. There is also a debate how infectious complications are considered and classified (fever, SIRS, symptomatic urinary infection, asymptomatic bacteriuria). Therefore it is difficult to compare the results of various studies or to draw definitive conclusions. The EAU guidelines give also no clear indication for the duration of antibiotic prophylaxis and when prophylaxis should be followed by prolonged therapy. Therefore urologists have to choose their practice according to their clinical experience (Table 4).

Consequently more patients may be imprudently exposed to the risk of infection, or, on the other hand, to over-treatment, which would also burden the health system.

When antibiotic prophylaxis is considered, its duration should be established prior to surgery. Duration may

### Table 6.
General risk factors for infection related to the patient.

- Elderly age
- Deficient nutritional status
- Impaired immune response
- Diabetes mellitus
- Smoking
- Overweight/obesity
- Co-existing infection at a remote site
- Lack of control of risk factors

### Table 7.
Increased risk factors related to increased bacterial load.

- Long term pre-operative hospitalisation or recent hospitalisation
- History of recurrent genitourinary tract infections
- Surgery involving bowel segments
- “Colonised” urinary tract
- Long-term urinary drainage
- Urinary obstruction
- Urinary stones
vary depending on the type of surgery or the type of antibiotic. Furthermore, prophylaxis should be administered only for a limited amount of time (not over 24 hours). The risk of post-treatment infection and sepsis is higher in immunocompromised patients or in patients with anatomical anomalies or diabetes mellitus with infection stones. Thus antibiotic prophylaxis and antibiotic therapy is agreed to be necessary. Latest studies have shown excellent results with fluoroquinolones both in prophylaxis and therapy of post-operative infection after percutaneous or ureteroscopic removal of stones. There is, however, still debate on the best No antibiotic prophylaxis modality prior to percutaneous or ureteroscopic removal and on its general usefulness prior to SWL.

We therefore hope that new studies will compare the various therapy regimens and analyse in more details the risk factors and economic aspects.

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INTRODUCTION

Since now extracorporal shockwave lithotripsy (SWL) is the treatment of choice for upper urinary tract stones (1, 2). SWL provides acceptable stonefree rates and a low morbidity of the treatment. But according to the stone mass and stone localization SWL leads to a high retreatment rate and disappointing results. Particular stones of the lower calix show low stonefree rates of about 50% (3). In addition stones of calyceal diverticula show low stonefree rates as well. In order to improve results of the treatment of lower pole stones and calyceal diverticulum stones endourological approaches are recommended. Since minimal invasive instruments had been invented, today it is possible to reach almost all parts of the calyceal system. Namely there are two main developments in endourology that have significant influence on the treatment of upper urinary stones. These are the retrograde flexible ureterorenoscopy (fURS) and the minimal-invasive percutaneous nephrolithotomy (Mini-Perc) (4). The aim of this paper is to report about the results of a high volume center of endourology and to compare the results to them of SWL.

SUMMARY

So far extracorporeal shockwave lithotripsy (SWL) is the treatment of choice for upper urinary tract stones. Since the introduction of new minimal-invasive endourological procedures, such as retrograde flexible ureterorenoscopy (fURS) and minimal-invasive percutaneous nephrolithotomy (Mini-Perc), alternative treatment modalities are available, which show enhanced stonefree rates and decreased treatment morbidity even in unfavorable stone localizations of the lower calix and calyceal diverticulum stones. In experienced hands modern endourological approaches are suitable as first-line treatment of upper urinary tract stones. Even in elderly patients and large stone burden the endourological techniques show acceptable results.

KEY WORDS: Urinary calculi; Ureteroscopy; Percutaneous nephrolithotomy.
time was 53 min. Stone-free status was determined by x-ray, ultrasound and endoscopic examination of the calyceal system. All patients got a DJ-stent for 10 days in order to prevent any ureteral obstruction. 88% of all patients were rendered stonefree. No major complications were observed. In 4.2% a pyelonephritis occurred and in 1.8% a mild perforation of the ureter was detected which healed without any ureteral alterations after temporary insertion of a DJ-stent. Average hospital stay was 2.2 days. If fURS is performed larger stone mass could be a limitation due to the fact, that all fragments have to be removed through the ureteral access sheath. This may lead to a longer operating time and may increase the rate of pyelonephritis and perforation. Therefore another prospective study was done in order to compare the results of fURS in patients suffering from a stone mass of less than 100mm² (group A) with those suffering from a stone mass exceeding 100 mm² (group B). Stonefree rate was 90.2% in group A and 88.2% in group B respectively. Retreatment rate of both groups was significantly different: 47% in group A and 11.9% in group B. There was a slight increase of mild complications. Perforations, which healed spontaneously, were observed in 2.6% (A) and 1.8% (B). Pyelonephritis was detected in 8% (A) and 4.2% (B). No major complications were seen in each of the both groups. This data shows, that even larger stone burden can be removed by fURS, if a slightly increased frequency of minor complications and an increase of the retreatmentrate is accepted. In summary, fURS in a high volume center can be recommended for primary treatment of upper urinary tract stones. Complication rate is comparable to that of SWL, but stonefree rate, even in unfavorable stone locations in the lower calix, is quite better. In addition fURS leads to a significant reduction of treatment time which is often the patient’s preference. Due to the fact, that fURS is not mentioned in all available national or international guidelines, fURS should be offered as first line treatment of upper urinary tract stones on patient’s preference and as second-line treatment in case of SWL failure.

**MINIMALLY-INVASIVE PERCUTANEOUS NEPHROLITHOTOMY**

In case of a large stone burden of the lower calix SWL shows poor results with stone-free rates of about only 50%. In case of SWL failure in these cases a percutaneous approach is recommended. So far a conventional percutaneous nephrolithotomy by means of a 26 or 30F nephroscope was performed. A conventional PCNL shows a high stonefree rate of about 85% but is associated with an increase of complication rate. Even severe bleedings leading to transfusions in up to 15% had been reported in the literature.
and some cases of loss of kidney had been reported (2). In order to combine the high stonefree rate of a percutaneous procedure with the low morbidity of SWL 6 years ago a new miniaturized nephroscope had been invented. First published in 2001 335 cases treated by Mini-Perc had been evaluated so far. Minimal-invasive percutaneous nephrolithotomy is performed by means of a new designed 12F nephroscope (Figure 3) (4). After puncture of the calyceal systems by ultrasound guidance a single step dilation is performed and a 15F Amplatz sheath is inserted (Figure 4). Lithotripsy is performed by means of a Holmium-laser. Laser-fibers with a diameter of 500µm are used. Stones are extracted by means of tipless nitinol baskets. To verify stonefree status and to check even small calices, an additional flexible nephroscopy is done by antegrade fURS. In 333 of 335 Mini-Percs (99.4%) the access to the calyceal systems had been established successfully (Figure 5). Mean stone size was 4.3 cm$^2$. Average operating time was 67min ± 30min. Overall stonefree rate 90.8%. Blood transfusions were neccessary in 1.9% of all patients. Pyelonephritis was observed in 6.5%. Except one arteriovenous fistula, which had been treated by interventional radiology, no mayor complications were observed. Using the Mini-Perc technique it was first questionable, whether patients successfully with larger stone burden can be treated as successful as those with smaller stone burden with the limited diameter of the Amplatz sheath. The results of Mini-Perc in patients suffering from large stone burden (8.9 cm$^2$) show comparable results: operating time 76min ± 30min, stonefree rate 91.3%, blood transfusion 1% and pyelonephritis 7.7%. Only retreatment-rate was significant different: 0.30 in all patients vs. 0.42 in patients with large stone burden. In addition invasiveness of Mini-Perc has been studied in patients aged 70 or more. 57 consecutive subjects had been evaluated and results had been compared to the average Mini-Perc population. No statistical difference had been found for stonefree rate, operating time, retreatment rate or morbidity of the procedure. Mini-Perc demonstrated to be well applicable in older patients. Results are independent of age in terms of stone-free rates and treatable stone burden. There was no higher morbidity in aged persons compared with younger individuals. Therefore, in aged patients Mini-Perc can be regarded as a safe and reliable alternative treatment modality to SWL and PCNL in suitable cases, as well.

In summary Mini-Perc can be recommended as a reliable technique in order to remove upper urinary tract stones with a diameter exceeding 1 cm. Complication rate is similar to SWL and fURS.

**DISCUSSION**

New miniaturized instruments provide an enhanced possibility to remove stones of the upper urinary tract. Namely there are two main endourological approaches which have to be discussed – this is retrograde flexible ureterorenoscopy and Mini-Perc. Both endourological techniques allow to receive an enhanced stonefree rate in comparison to SWL, which is the treatment of choice of calyceal stones so far.

**Figure 3.**
Comparison of miniaturized and conventional nephroscope.

a. Mininephroscope.
b. Conventional nephroscope.

discussion

New miniaturized instruments provide an enhanced possibility to remove stones of the upper urinary tract. Namely there are two main endourological approaches which have to be discussed – this is retrograde flexible ureterorenoscopy and Mini-Perc. Both endourological techniques allow to receive an enhanced stonefree rate in comparison to SWL, which is the treatment of choice of calyceal stones so far.
Particularly lower pole stones and calyceal diverticulum stones can be treated by endourology more effectively than by SWL (12). The success rate of all stone treatment modalities is compared by the stone-free rates. In this context one has to consider, that the stone-free status after endourological techniques is determined by endoscopic evaluation of the calyceal system whereas stone-free rate after SWL is determined by x-ray or ultrasound examination (11). So called “clinical insignificant residual fragments” (CIRF), which are accepted as a success of SWL, do not occur after endourological procedures. As stone-free status is determined by endoscopic examination of the calyceal system, definition of stone-free after endourological procedures is quite more precise. In addition papillary calcifications, which adhere to the renal tissue and cannot be removed, are often detected in endourology of the upper urinary tract. These calcifications can be identified by endourology and need not to be treated. In SWL it often remains unclear, whether residual calcifications are treatable or not.

The morbidity of the new endourological approaches of the upper urinary tract is comparable to the morbidity of SWL. After SWL hematomata of the kidney are detected in up to 1.5%. The main reason for the low morbidity of the endourological approaches is the fragility and miniaturation of the instruments. Often the probability of damaging the instrument is higher than altering the patients urinary tract (13, 14). Of course the experience of the surgeon plays a very important role in the frequency of complications. The data mentioned above is collected from a high volume center in endourology, where about 700 ureteroscopies and 150 Mini-Perc procedures are performed each year. But the fact, that a significant part of the presented data is derived from patients, which had been treated by residents in training under supervision, shows, that the learning curve of minimally invasive endourological procedures is very steep and low morbidity of the procedures can be achieved from any center elsewhere.

As the indications for fURS and Mini-Perc are overlapping, it is suitable to discuss the main advantages and disadvantages of both techniques (Figure 6) (12). According to the stone mass, fURS is suitable for stones up to 1 cm and Mini-Perc for stones exceeding 1 cm. The approach of fURS is facilitated by ureteral access sheaths whereas Mini-Perc requires high experience to establish the percutaneous tract. fURS is superior to stones of the mid and upper calix. Mini-Perc is best for lower pole stones. Holmium-laser-Lithotripsy is a precondition for fURS, in Mini-Perc ultrasound and ballistic lithotripsy can be used as well. fURS may be a high-cost procedure as instruments are very fragile and expensive (13, 14). Disorders in hemostasis may allow to perform fURS as Mini-Perc is contraindicated in these cases. Finally all aspects discussed so far can be transferred to the endourological treatment in children. Even in children, where anatomical conditions are very limited, miniaturized instruments are suitable. Morbidity of treatment and success rate are comparable to those in adults (15).
CONCLUSION

Retrograde flexible ureterorenoscopy and Mini-Perc offer new possibilities for upper urinary tract stone treatment. In comparison to SWL, these endourological techniques provide an enhanced stone-free rate and a low treatment morbidity, which is comparable to SWL. Although SWL is the treatment modality of choice for upper urinary tract calculi so far, the significance of advanced endourological approaches for the upper urinary tract is increasing more and more. Reduced treatment time, enhanced stone-free rate and low morbidity perhaps will lead to endourological stone removal of the upper urinary tract as a primary approach.

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INTRODUCTION

Surgical management of stones in anomalous kidney presents a problem for urologic surgeons. Various minimally invasive management options have been previously reported including shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL), as well as ureteroscopy. While all of their techniques work well in select populations, recent improvements in endoscopic technology and intracorporeal lithotripsy make ureteroscopy possible for most cases of stones in ectopic, pelvic, or transplant kidneys. Additionally, many of the limitations of shock wave lithotripsy and/or percutaneous nephrolithotomy can be overcome with a ureteroscopic approach.

As new endoscopic technology and adjunctive device developments continue to enter the urologist’s armamentarium, the role of ureteroscopy continues to expand. Once unapproachable stones may now be addressed via flexible ureteroscopes, improved baskets, and holmium lasers. In conclusion, ureteroscopic management of urolithiasis in anomalously located kidneys is a viable approach. Success rates are similar to those reported for SWL and the morbidity is less than PNL. With increasing dissemination of ureteroscopic skills, improved technology and enhanced adjunctive devices (i.e., sheaths and baskets), ureteroscopy should play a larger role in the management of these challenging patients, with subsequently reduced patient morbidity.

KEY WORDS: Renal; Kidney; Nephrolithiasis; Ectopic; Pelvic kidney; Horseshoe; Ureteroscopy.


METHODS

The ureteroscopic approach to anomalous renal units is similar to that for normally positioned kidneys. Preoperative planning with appropriate imaging is essential. Intravenous pyelography and/or a CT urogram provides the urologist with a vital understanding of the anatomic challenges associated with stone removal. Intra-operatively fluoroscopy should be utilized to confirm pre-operative findings and position of calculi. Retrograde pyelogram, performed in the operating theater, permits real time assessment and allows for future comparisons of ureteroscopic positioning. As with all ureteroscopic procedures, appropriate access to the intra-renal collecting system is critical. The use of a safety wire and/or a working wire assures access throughout the operation. If necessary an appropriate sized ureteral access sheath may be beneficial during ureteroscopy in anomalous kidneys. The malpositioned renal collecting system often leads to a tortuous ureter. In these cases, an access sheath can “straighten” the ureter in addition to the...
advantages of decreased renal pressure and rapid, repeated passes of the ureteroscope into the renal collecting system. The corner stone of these challenging procedures is the flexible ureteroscope itself. Due to the serpentine route of the ureter and the abnormal orientation of the renal pelvis, the flexible ureteroscope is indispensable. Once inside the renal pelvis, both active and passive deflection can be utilized to gain entrance to virtually all calyces. The holmium laser is the preferred method of calculus fragmentation after identification of the stone. If the laser cannot be passed through the scope due to the angle of deflection, a nitinol basket or grasper may aide in repositioning the stone into a more accessible location. At the completion of the procedure, a ureteral stent may be necessary depending upon the surgeon’s assessment. Stents are beneficial in the presence of residual stone fragments, if repeat ureteroscopy is planned, or if there is any damage or inflammation of the ureter. Follow-up with post-operative imaging should be performed to determine if any stone fragments remain and to assess functional status of the anomalous kidney.

RESULTS
Currently, ureteroscopic intervention for stones in congenitally anomalous kidneys has been documented for only a small number of patients. These renal anomalies comprise horseshoe kidneys, pelvic kidneys and a crossed ectopic kidney (L-configuration). These cases have been reviewed in 3 previous publications including a case report, a scientific abstract, and a multi-center retrospective review (1-3). The patients’ stone burden ranges from 1 to 3 calculi per renal unit with an overall mean of 1.3 stones per unit. Overall mean stone size for these patients equals 12.2 mm, ranging 3 mm to 25 mm, at greatest dimension. A total of 27 previous procedures were executed prior to performance of the ureteroscopic procedures, including shock wave lithotripsy and percutaneous nephrolithotomy for a mean of 1.4 procedures per patient prior to inclusion. Patients were evaluated post-operatively with nephrostograms, intravenous pyelogram or CT scan. Forty four percent were deemed stone free (no evidence of residual stone burden) after a single intervention. An additional 31% of patients required a second ureteroscopic procedure to clear residual fragments, yielding a 75% stone free rate for the population, overall. Another 12.5% of patients had residual stone fragments < 2 mm in diameter.

DISCUSSION
Abnormalities of form, fusion, and ascent during fetal development result in anomalous renal units. The most common abnormality is horseshoe kidney (HSK) occurring in 1 in 400 to 1 in 666 people (4-5). Pelvic Kidneys (PK) are even less common, occurring in about 1 in 900 people (4). Fewer than 1000 cases of crossed ectopic kidney (CEK) with or without fusion have been documented in the literature (4). Iatrogenic pelvic kidney secondary to renal transplantation (RT) represent an increasing source of anomalous kidneys. Over 18,000 kidney or kidney/pancreas transplants were performed last year in the United States alone (6). The incidence of urolithiasis in patients with anomalous kidneys is higher than that of the general population. Patients with HSKs have an approximately 20% associated risk of stone formation (7-8). It is well accepted that the abnormal anatomic positioning of the kidney and associated renal pelvis leads to urinary stasis, dilation of the collecting system and the subsequent formation of stones (4). These risk factors can likely be applied, as well, to the anomalies of PKs and CEKs. However, anatomic variation is not the sole cause of stone formation in these patients. In a review of patients with stones in HSKs, all patients were found to have metabolic derangements on during metabolic evaluation (9). The most prevalent derangement in these patients was hypertriglyceridemia. While the metabolic risk factors for urolithiasis in patients with PKs and CEKs have not been documented, it is a fair assumption that these patients would also have urinary derangements which contribute to their disease.

Controversy has existed regarding stone formation in transplant recipients. While some reports indicated increased rates, more recently authors have demonstrated a decreased rate of urolithiasis (10-12). A recently reported study suggests a stone formation rate of 0.4% to 1% (12). Transplant recipients have been shown to have metabolic abnormalities, most commonly gout. Additionally, secondary hyperparathyroidism and recurrent UTI’s are often associated with stone disease in renal transplant patients.

Surgical management of urolithiasis in patients with anomalous kidneys provides a significant challenge to urologists. Traditionally, these patients have been treated with percutaneous approaches (PNL) and/or with shockwave lithotripsy (SWL). Stone free rates for HSKs treated via SWL average 67.8% and have a high re-treatment rate (3). Percutaneous surgery has been demonstrated to have a higher stone free rate, generally greater than 75% for horseshoe kidneys (13, 14). Patients with pelvic kidneys have stone free rates comparable to that of the general population, 82% in the largest series, but like HSKs require a greater number of secondary procedures (15). In general, PKs are not managed by percutaneous surgery because of overlying viscera, however case reports and small series of laparoscopic-assisted percutaneous approaches have been reported with adequate success. These approaches, SWL and PNL, are accepted as the standards for patients with renal transplant kidneys, depending upon stone size. Similar to the general population, stones less than 2 cm can be managed with SWL and those greater than 2 cm should be approached percutaneously (12, 16).

While SWL and PNL are acceptable approaches to anomalously located kidney, they are not always medically or technically feasible. Obesity, deformities of body habitus, abnormal renal anatomy, associated coagulopathy, and uncontrolled hypertension may limit the use of SWL. Additionally, large (> 2 cm) or lower pole/dependent stone burdens will be sub-optimally treated with SWL. Patients with severe cardiopulmonary disease, coagulopathy, or inability to tolerate prone positioning are likely not
to be candidates for PNL. Serious consideration must be given to the use of ureteroscopy in these complex patients. Technotologic innovations continue to increase the ease and success of ureteroscopy. Smaller flexible ureteroscopes with improved active deflection allows access to all regions of the intra-renal collecting system. Enhanced optics and digital technology provide the urologist greater confidence in identification of renal anatomy and stone burden. Small holmium laser fibers function as an effective lithotripter. The use of ureteral access sheaths (UAS) aids in the ability to approach anomalous kidneys. Access sheaths “straighten” the ureter permitting easier access to the renal pelvis (3). Additionally, UASs allow multiple rapid passes of the ureteroscope to remove calculi. The use of UASs in the setting of stone baskets, decreased intrarenal pressures, protection to both the ureter and scope, and improved visualization via peri-ureteroscope drainage of debris.

Despite the advancements of ureteroscopy, there is little in the published literature regarding its use in anomalously located kidneys. The largest reviews addressing this issue reviewed 8 patients (4 HSKs and 4 PKs) treated ureteroscopically due to co-morbid conditions limiting the use of other approaches (3). The stone free rate in this series was 75% for both HSKs and PKs while 88% of patients were asymptomatic after their procedure. Furthermore, none of the patients in the study required repeated surgical intervention and there were no intra-operative or post-operative complications. There is even less data reported regarding crossed ectopic kidneys. One patient was included and successfully treated with ureteroscopy (2). Additionally, a case report of 2 patients treated via SWL required one patient be treated ureteroscopically to attain successful clearance of the stone burden (17). For patients with renal transplant kidneys, two reports have documented significant success rates with retrograde ureteroscopy, 67% to 86% (18, 19). However both authors caution regarding the possible difficulty in identifying and cannulating the implanted transplant ureter. Ureteroscopic management of urolithiasis in anomalously located kidneys is a viable approach. Success rates are similar to those reported for SWL and the morbidity is less than PNL. With increasing dissemination of ureteroscopic skills, improved technology and enhanced adjunctive devices (i.e.; sheaths and baskets), ureteroscopy should play a larger role in the management of these challenging patients, with subsequently reduced patient morbidity.

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INTRODUCTION

Extracorporeal shock wave lithotripsy (SWL) is a well-established procedure for renal and ureteral stone treatment. The first clinical application of SWL dates back to 1980 in Germany. SWL gained a rapid and global acceptance and more than 5,000 lithotripters are in use today for more than a million treatments worldwide (1).

Treatment of renal and ureteral stones by SWL has been proved safe and effective in the last 25 years. We reviewed our twenty-four year experience, which began in January 1985 with an original HM3 Dornier lithotripter and has continued along the years with second and multifunctional third generation lithotripters.

SWL AND RENAL DAMAGE

Many studies have been carried out to investigate possible parenchymal damage by shock waves. In the immediate follow-up, reported incidence of symptomatic renal
Haemorrhage was between 0.2% and 1.5%, (5-7), but when a CT or MRI scan was performed after SWL the rate increased to as high as 20-25% (8).

Histopathological tubular and endothelial cell damage on arteries, veins, and glomerular capillaries have also been demonstrated. Blood and urinary markers of acute renal damage such as renin, creatinine, N-acetyl-glucosaminidase, b-galactosidase, b-2-microglobulin, and proteinuria can be detected immediately after SWL and return to normal within a few days (9-11). The NAG rise within a few hours, peaks, and returns to normal in 4 to 7 days (12).

To determine whether this acute damage could have clinical relevance in inducing chronic effects, we studied the short-term and long-term (12-56 months) effects of SWL in a group of 52 patients treated on a solitary kidney. No significant increases in serum creatinine were found even at the long-term follow-up, and only one previously normotensive patient developed hypertension. In our experience, the demonstrated effectiveness and lack of sequelae at long-term follow-up confirmed that SWL is not only effective but also safe even for treating renal stones in solitary kidney (13).

HYPERTENSION

Some retrospective studies have reported an incidence of new-onset hypertension of between 2.4% and 8.1% (14-16), and a significant rise in mean diastolic blood pressure has been observed by some Authors (17-18). The rise in diastolic blood pressure remained statistically significant even when other significant pre-existing risk factors, such as years since treatment and direct shock wave exposure to the kidney, were considered (19). Our prospective study, along with others, did not show any changes in blood pressure after SWL (20-22). In a 24 to 36 month prospective study we followed 68 patients treated for renal stones, to assess the risk of hypertension. In our experience, new-onset hypertension was not more common than what was statistically expected. This prospective study on a small number of patients did not demonstrate any significant mean diastolic blood pressure rise at long-term follow-up (20).

A 45% rate of new-onset hypertension was demonstrated in a group of patients older than 60 years and it was suggested that these patients were prone to develop hypertension at a higher rate than the control population (23). More recently, hypertension has been related to renal stone disease rather than to the treatment (24).

CARDIAC DYSRHYTHMIAS

The occurrence of cardiac dysrhythmia during extracorporeal treatment by a spark-gap generator is a well-known complication. For this reason, the release of the shock wave was synchronized with the refractory phase of the cardiac cycle. Using this procedure, the rate of dysrhythmic occurrences reported ranged from 0.3% to 1% (25-27) With lithotripters that use a piezoelectric source, following continuous ECG monitoring, the treatment induced or aggravated cardiac dysrhythmias in 20% to 59% of patients (28, 29). Using different electromagnet-ic lithotripters without triggering, the percentage of dysrhythmias ranged from 1.4% to 9% (30-33).

We evaluated the incidence and gravity of dysrhythmic complications during non-synchronised SWL using an electromagnetic lithotripter. The percentage of dysrhythmia episodes was 8.8% in patients with no previous cardiac arrhythmias, with an incidence of 5.6% of ventricular dysrhythmia, without any significant clinical effects. It was sufficient to interrupt the treatment momentarily to obtain resumption of the normal rhythm. The dysrhythmias occurred almost exclusively in stone kidney treatments and never in distal ureteral ones. No significant correlation was found between the side of the treated kidney, the number and strength of shockwaves, or the administration of analgesics and the occurrence of dysrhythmia. In conclusion SWL without ECG triggering was not associated with the occurrence of dysrhythmia episodes of any particular clinical significance, but continuous monitoring of cardiac activity during treatment remains advisable because it makes it possible to identify any alterations promptly (34).

SWL AND INFECTIVE COMPLICATIONS

Bacteriuria after SWL was reported in 7.7-23.5% of patients (35-36). The fact that urine was found to be sterile before SWL did not always vouch for a hyperpyrexia-free post treatment course (37). Bacteria have been shown to be present on the surface of the calculi as well as within the stones themselves (38). In the majority of such cases, the examination of cultures led to identification of Gram-negative bacteria. As is well known, Gram-negative bacteria produce pyrogenic endotoxins which could enter the system via the microlesions resulting from lithiasic extracorporeal treatment and explain post-SWL hyperpyrexia. In our prospective study we followed 150 patients with previous negative urine culture, treated with SWL for renal stones of less than 15 mm in diameter. The urine culture was checked on the 3rd and 30th day after treatment. The first test, on the 3rd day, revealed 7.3% of positive urine cultures but only 3.3% presented a symptomatic infection with hyperpyrexia (> 38°C). In most cases the pathogens we identified were Gram negative. All patients whose urine culture tested positive received antibiotic treatment. At thirty days all urine cultures tested negative. Our therapeutic approach in the case of patients with simple renal stones, negative urine culture, and no history of previous urinary tract infection, is to cure infective complications if they occur, with no pre-treatment antibiotic prophylaxis. When predisposing factors as pre-existing urinary tract infection (UTI), infected or multiple stones, history of recurrent UTIs, or urinary obstruction are present or when pre-treatment manoeuvres are planned, a prophylactic antibiotic is advised (39).

SWL CLINICAL EXPERIENCE

Renal stones

The size of stones, in addition to their site, has been used by numerous authors to divide patients with stones into categories and better evaluate the potential and limits of
extracorporeal lithotripsy. Although there is no universally accepted system of measurement, an evident direct correlation exists between results and stone size. The stone free rate varies with different lithotripters in the various series: 90-56% for stones of maximum diameter <1 cm, 78-30% for stones between 1 and 2 cm and 52.5-10% for stones between 2 and 3 cm (40). In recent series, the overall efficacy of the SWL treatment was reported as amounting to between 81% and 86.7% of stone free patients (41, 42). For staghorn stones extracorporeal lithotripsy as monotherapy has allowed a stone free rate varying between 24% and 55%, with a high percentage of residual fragments in about 50% of cases in the various series. Combining percutaneous and extracorporeal lithotripsy, the stone free rate rises to 59-74% (43, 44). The sandwich therapy reduces the rate of residual fragments and the elevated risk of regrowth of the stones in these patients. We followed for an average of 42 months patients treated with SWL for different types of stones (45). At discharge, 31.5% of the patients were stone free, whereas 65.3% had stone dust or passable fragments. At three-month follow-up, 64.8% were stone free and 33.6% had dust or passable fragments. After a follow-up of over 24 months (mean 42 months), 55% of the patients were still stone free, recurrence was observed in 13.8% and regrowth of fragments in 22.3% of the patients. Positive urine culture was found in 16% of the patients at follow-up. The regrowth of residual fragments after discharge in infected patients was 65%. The incidence of new hypertension in this series was 6.1%. Our longer follow-up (mean 90 months) on 210 patients showed overall recurrence and regrowth to be 28% and 48%, respectively (unpublished data).

Adding the percentage of true recurrence reported by the various authors at 19 to 42 months follow-up (6.2-13.8%) to the fragment regrowth rate (17.2-22.3%) gives a total new stone rate of 23.4% (46) and 36% (45) for two of the series considered. These figures do not differ greatly from those reported in a population of untreated stone formers (10-15% per year) (47-49).

Extracorporeal lithotripsy thus seems not to influence lithiasis recurrence significantly. However, it is useful to perform a metabolic study on patients undergoing SWL to identify patients at high risk of stone recurrence and take adequate prophylactic measures (12, 47, 50). In our experience on 316 caliceal stones treated with an electrohydraulic lithotripter, the stone free rate was 84%, 69%, and 58%, respectively, for stones of the upper, mid, and lower calices. The presence of caliceal neck stenosis has a marked effect on outcome, reducing the stone free rate to 26%, 39%, and only 18% for upper, mid, and lower caliceal calculi, respectively (39).

With respect to the success of SWL treatment, we must consider two issues: the success rate and the rate of regrowth of fragments. The SWL success rate seems to be directly related to the site of the stone. Renal pelvis and upper and medial calyx stones are more frequently cleared than stones in a lower calyx or multiple or staghorn stones and fragments in the latter sites demonstrated a worse clearance and a high rate of regrowth. With respect to the fragments, we observed that patients with fragments still present after 3 months of follow-up were unlikely to be cleared in a longer follow-up; in fact, only 9.4% of the patients with fragments at 3 month follow-up were stone free after 24 months (45).

Ureteral stones
The type of imaging used during treatment has an effect on the efficacy of ureteral stone treatment. Lithotripters with radiological or mixed (radiological and ultrasound) imaging have produced better success rates: 70-96%, 71-87.7%, and 71-91.7 for upper, mid, and lower ureteral stones, respectively (51-53). However, stone free rate after a single SWL treatment is lower than for kidney stones and the re-treatment rate is higher (54). A higher success rate has been reported for upper and mid ureteral stones compared to distal ones (55). In an AUA meta-analysis, better results were reported in ureteral stones <10 mm with a 74% stone free rate compared to 46% for 10-20 mm stones (56). In our experience, 209 patients underwent 327 treatments with a third-generation electromagnetic shock wave lithotripter (Storz SLX). The stones were located in the upper third of the ureter in 94 patients (45%), in the mid ureter in 20 patients (10%) and the distal third in 95 patients (45%). At three month follow-up, 190 out of 209 patients were stone free (91%). Out of the patients successfully treated, 59% were stone free after just one treat¬ment and the percentage rose to 87% after the second treatment. No major complications were observed in the follow-up. The success rate after the first treatment was 52%, 59%, and 66% for the upper, mid, and distal ureter, respectively. This study also proves a significant correlation between failures and re-treatments and stones greater than 10 mm in diameter. Our experience, with an electromagneti c lithotripter, confirmed the feasibility and efficacy of the in situ treatment of ureteral stones. Pre-treatment manoeuvres are reserved for patients in whom urinary tract is obstructed or to relieve colic. In our opinion, the possibility of performing treatment without anaesthesia, the absence of important complications, and the high rate of success makes extracorporeal lithotripsy the treatment of choice for ureteral stones (57).

Easy access to the treatment, because of its low invasiveness and the number of lithotripters located in hospitals and clinics, should not, however, lead to an inappropriate use of this treatment method. Adequate evaluation of the patient and the stone (composition and size) is required, and all possible treatment options should be considered. Ureterorenoscopy with high success rates, low complication rate, and immediate complete stone removal is in most cases a very attractive alternative in endourological stone treatment.

SWL IN PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS
The most frequent effect of SWL is haematuria, because the risk of perirenal haematomas, congenital and acquired defects of homeostasis were considered an absolute contraindication to SWL treatment. Patients who are receiving antithrombotic agents affecting platelet function are at high risk for haemorrhagic complications (58-59).
However, over the years several patients with homeostasis disorders have been treated successfully (60-62). We treated 23 patients who were receiving antiplatelet agents because of various cardiovascular conditions, 19 with renal and 4 with ureteral stones. We divided these patients into two groups: Group 1 had a low thromboembolic risk and Group 2 had a high thromboembolic risk. Group 1 patients discontinued their antiplatelet therapy 8 days prior to SWL to allow for a sufficient number of functioning platelets. Group 2 patients suspended antiplatelet therapy and unfractioned heparin 5000 IU tid was administered for the 8 days prior to SWL. On the ninth day of withdrawal, SWL was performed in all patients. The anithrombotic therapy was reintroduced in all patients within 10 to 14 days from withdrawal. A close follow-up was performed during the postoperative period. No haematomas and thromboembolic events were observed. Our strategy for the suspension or substitution of antiplatelet therapy allowed us to perform SWL without haemorrhagic or thromboembolic complications. Extracorporeal lithotripsy carried out with tailored precautions proved, in our experience, to be effective even in patients with a higher haemorrhagic risk (63).

RENAL STONE FRAGMENTS
The fate of residual fragments represents a common and still controversial problem of extracorporeal treatment. Although efficacious fracture of stones into fragments less than 5 mm has been described, 85% of patients have been reported to have residual fragments when discharged from the hospital; 3 months after extracorporeal treatment, residual fragments are present in 24 to 36% of patients (45, 64, 65). Small fragments less than 5 mm are defined as clinically insignificant residual fragments (CIRF); although they are likely to pass spontaneously and remain asymptomatic, they are considered by some authors a factor that favours regrowth and an increased risk for symptomatic episodes (66-68). We described a select group of asymptomatic patients with fragments and dust 3 months after SWL, who were followed to evaluate the long-term outcome and therapeutic implications. A total of 129 patients with dust and residual fragments at 3 months were re-examined at 12 months, whereas 12 were lost to follow-up; 95 were also evaluated at 24 months. Follow-up examinations consisted of radiographic studies, renal ultrasound, and urine culture. Dust and residual fragments were sought, and patients were defined as stone free or as having persistent lithiasis or stone regrowth. Recurrences in the stone free patients at 12 months were also considered at the 24 month follow-up. At the 12-month follow-up, 60 patients (46.5%) were stone-free and 56 (43.5%) still had dust or residual fragments. The localisation of the stones or fragments at 3 months and their sizes did not have a significant influence on the stone free rate, but regrowth was greater in patients with stones larger than 10 mm (27.5% versus 2.2%). The chance of eliminating residual stones at 12 months was significantly greater in patients with dust than in those with residual fragments (58% versus 36%). A total of 15 patients (11.6%) had symptomatic episodes in the first year of follow-up. Overall, 14.7% of the patients had symptomatic events or required further treatment in the first year of follow-up. In the second year of follow-up, 7.3% of patients complained of pain symptoms. In this group of patients, spontaneous elimination of fragments, particularly dust, was good at 12-month follow-up (46.5%). This rate, better than in other series, may be attributable to the selection of single stones less than 15 mm with normal renal morphology. At 24-month follow-up only a further 8.5% of the patients became stone free. Fragment regrowth was observed in 17% of the patients, particularly those who had pre-treatment stones greater than 10 mm and those who still had a positive urine culture at 12 months. Patients with fragments do not require systematic retreatment but they could be followed and treated if necessary if stones recur or symptoms persist (69). Most of the CIRF pass spontaneously after treatment without any complication, but since about 20% of patients become symptomatic or require intervention, a close follow-up is required (70, 71).

CONCLUSION
Twenty-five years after the initial clinical experience of extracorporeal shock wave lithotripsy, no doubts remain as to its efficacy in treating ureteral and renal stones. Furthermore, important and impressive advances have been made, with a marked influence on its clinical application, and SWL may be performed on an outpatient basis without any sedation. The side effects that have been reported are rare and do not interfere with the effectiveness and safety of this method. Extracorporeal shock wave lithotripsy is the first choice treatment today for most renal and ureteral stones, however adequate evaluation of the patient and of the stone is required, and all possible treatment options should be considered.

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Introduction

Following its clinical introduction in early 1980’s; shock-wave lithotripsy (SWL) has become the preferred treatment modality in the majority of symptomatic urinary calculi with its safe and effective results (1, 2). However, despite its marked effectiveness, the treatment was not completely free from side effects and in the last two decades more and more investigators have questioned the adverse effect of this technique with experimental as well as clinical studies. Although the main target of the shock waves is the stone located in the kidney, the surrounding tissue or other organs may also be subjected to trauma during this procedure (3-6).

Concerning the acute histopathologic changes after high energy shockwave (HESW) application, in addition to local side effects such as perirenal and subcapsular hematoma formation, animal studies have revealed corticomedullary and interstitial hemorrhage, tubular dilatation with hydroptic or vacuolar degeneration, focal interstitial glomerulonephritis, and mononuclear cell infiltration (7-10). On the other hand, glomerular atrophy, tubular necrosis, thickening of capsule and parenchymal fibrosis constituted the chronic histologic alterations as demonstrated by several studies (1, 6, 7). Last but not least, transient decrease in effective plasma renal flow (EPRF) along with the increase in urinary excretion of some small proteins has indicated proximal

Prevention of shockwave induced functional and morphological alterations: An overview.

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Summary

Experimental as well as clinical findings reported in the literature suggest that treatment with shock wave lithotripsy (SWL) causes renal parenchymal damage mainly by generating free radicals through ischaemia /reperfusion injury mechanism. Although SWL-induced renal damage is well tolerated in the majority of healthy cases with no permanent functional and/or morphologic side effects, a subset of patients with certain risk factors requires close attention on this aspect among which the ones with pre-existing renal disorders, urinary tract infection, previous lithotripsy history and solitary kidneys could be mentioned. It is clear that in such patients lowering the number of shock waves (per session) could be beneficial and has been applied by the physicians as the first practical step of diminishing SWL induced parenchymal damage. On the other hand, taking the injurious effects of high energy shock wave (HESW) induced free radical formation on renal parenchyma and subsequent histopathologic alterations into account, physicians searched for some protective agents in an attempt to prevent or at least to limit the extent of the functional as well as the morphologic alterations. Among these agents calcium channel blocking agents (verapamil and nifedipine), antioxidant agents (allopurinol, vitamin E and selenium) and potassium citrate have been used to minimize these unestimated adverse effects.

Additionally, therapeutic application of these agents on reducing stone recurrence particularly after SWL will gain more importance in the future in order to limit new stone formation in these cases. Lastly, as experimental and clinical studies have demonstrated, combination of anti-oxidants with free radical scavengers may provide superior renal protection against shock wave induced trauma. However, we believe that further investigations are certainly needed to determine the dose-response relationship between the damaging effects of SWL application and the protective role of these agents.

Key words: Shock Wave Lithotripsy; Calcium channel blocking agents; Antioxidant agents; Renal damage.

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and tubular dysfunction produced by HESW (3, 11-14). In contrast to normal healthy subjects who require one or two sessions for a successful outcome, all these aforementioned HESW related adverse effects have been found to be important and critical in patients with solitary kidney or impaired renal function, patients requiring multiple sessions with higher numbers of shockwaves and elderly and pediatric patients. Taking all these unestimated histopathological alterations at different levels (tubular, glomerular, interstitial) into account, the physicians began to lower the energy level, apply a decreased number of shock waves in one session or look for some protective agents to limit the extent and the severity of functional as well as morphological alterations (15).

In this present paper we review agents that have been used in an attempt to limit SWL related functional and morphologic changes as well as the possible increased stone recurrence rates after this type of management.

**SHOCKWAVE DAMAGE: MECHANISM OF ACTION**

Concerning the mechanism of the adverse effects of ESWL, although initially they were attributed to renal damage resulting only from the direct action of cavitation bubbles or shear stress originating from shock-wave energy (13, 15), more recently free radical formation originating from transient ischemia due to HESW application was considered to be an integral element in shock wave-induced renal damage through an indirect mechanism. Related with this subject, vascular injuries inducing tissue edema and hypoxia produced by the direct traumatic effects of HESW have been noted in in-vivo experiments. Studies again have clearly demonstrated that renal parenchymal ischemia secondary to HESW application may be related to the decrease in EPRF together with an intrarenal (parenchymal) obstructive pattern without obstructive hydronephrosis (16). As a result of ischemia formation and free radical generation, lipid peroxidation and the disruption of cellular membranes will in turn induce calcium overload and initiate the process of cellular death. Thus, free radical formation and subsequent damage to the kidney during the procedure seem to be similar to the chain events in the ischemia-reperfusion models (17-21). Treatment with free radical scavenger enzymes (superoxide dismutase) has been found to be effective in terms of survival and renal function (22, 23). In conclusion, in the light of the findings reported in the literature, it is clear that SWL induced renal trauma can occur as a result of multiple mechanisms among which small vessel injury, production of free radicals and the subsequent damage induced by lipid peroxidation could be mentioned as the contributing factors in shock wave-induced renal parenchymal injury (15, 19, 21-26).

**PREVENTION OF SHOCKWAVE-INDUCED RENAL DAMAGE**

Taking the injurious effects of HESW on renal parenchyma and histopathologic alterations including apoptotic changes in renal tubular epithelium (as a result of free radical production) into account, physicians searched for some agents in an attempt to prevent or at least to limit the extent of the functional as well as the morphologic alterations. Among these agents calcium channel blocking agents (verapamil and nifedipine), antioxidant agents (allopurinol, vitamin E and selenium) and potassium citrate have been used to minimize the established effects of free oxygen radical formation in renal parenchyma.

**PROTECTIVE AGENTS**

1. **Calcium antagonists**

Preservation of renal functional and morphological integrity

Calcium antagonists (a heterogeneous group, which include three main classes, namely phenylalkylamines, benzothiazepines and dihydropyridines) have been found to be successful in limiting the ischemia-induced alterations in target organs such as heart and kidney by lowering the blood pressure mainly through vasodilation and reduction of peripheral resistance to increase renal blood flow for the maintenance of normal tissue physiology (27-30). In addition to the several studies indicating the protective role of these agents in certain models of ischemia-induced acute renal failure, investigations with Madin Darby Canine Kidney (MDCK) cells have also demonstrated similar effects of calcium entry blockers against shockwave-induced tubular dysfunction as well as renal parenchymal damage in both humans and animal models (29, 31, 32). Although the underlying mechanisms are not clarified yet, authors have stated that along with the possible direct actions on tubular cells, this specific effect may be attributed to their regulatory role on blood distribution during possible transient ischemia induced by HESW (33-38). Decrease in blood pressure and improvement of renal capacity and hemodynamics were main effects of these agents making them effective enough in preserving renal morphology and function. However, in addition to the vasodilatory effect of these agents, prevention of calcium influx into injured cells may be responsible for these specific effects (28, 30).

In a previously performed experimental study, we were able to demonstrate the protective effect of verapamil against the adverse effects of shock waves in terms of crystal deposition in traumatized tissue and new stone formation as well as tissue protection. By lowering the risk of renal morphological changes after shock wave application, verapamil may be effective during long-term follow-up to limit the risk of crystal deposition and subsequent crystal formation and/or regrowth (39). Concerning the reno-protective role of calcium antagonists, there are two main strategies defined in recent years to have a maximum efficacy in certain pathologies among which urinary stone disease has a specific place to care. First, pharmacologic intervention aimed at reduction of blood pressure and secondly, dietary intervention aimed at reduction of protein intake. In addition to its specific protective effects on renal morphology and function, the high incidence of hypertension among stone forming patients will make verapamil further effective in preserving renal integrity by aforementioned mechanisms (31, 40).
Related with this subject of the calcium channel blocking agents, nifedipine has been found to limit calcium phosphate stone formation induced by a high-cholesterol diet in rats (33); Mason et al. have recently showed that, amlodipine can regulate membrane fluidity and cholesterol deposition, stimulate nitric oxide (NO) production to recruit its biologic actions, act as an antioxidant, and regulate matrix deposition (41).

Finally, glucosaminoglycans (GAGs) have been found to be protective on shockwave induced morphological changes by some possible mechanisms among which mechanical restoration of glomerular charge density, preservation of glomerular basement membrane thickening and restoration of GAG metabolism could be mentioned (42).

Prevention of crystal deposition and stone re-growth
Studies dealing with the unestimated morphological traumatizing effects of HESW on renal parenchyma have shown that high energy shock wave induced chronic alterations may also be responsible for future crystal deposition and stone formation (42-44). Among the chronic alterations observed after shockwave application, patchy fibrosis of the renal parenchyma, new onset of hypertension and increased stone recurrence and regrowth rates have constituted the most debated features (6). Recurrence rates of 6% after 1 year and 20% after 4 years as reported in the literature indicate the importance of the subject (43). Concerning the stone recurrence rates after HESW application, although the traumatizing nature of SWL has not been well evaluated, in our study we were able to show the possible increased crystal deposition in traumatized tissue after HESW application in rabbit model(s).Thus, it is clear that every traumatic effect on renal parenchyma causing fibrotic changes of tissues including patchy fibrosis of the renal parenchyma after HESW application may constitute a meaningful basis for new stone formation, in other words stone recurrence. In the light of these facts, it is obvious that limitation of renal parenchymal fibrosis occurring as a result of HESW application will reduce the risk of stone recurrence by lowering the chance of lithogenic foci formation. Pre-medication with verapamil has been found to be protective enough against shock-wave induced renal trauma and damage, which in turn may be responsible for subsequent possible crystal deposition (33, 36, 37, 46, 47). The limiting effect on crystal deposition and the minimizing effect of ischemic episodes may account for the protective effect of verapamil or other calcium channel blockers on kidneys undergoing HESW-induced trauma. Prevention of renal parenchymal ischemia formation causing tubular damage may also contribute to this specific and protective effect of calcium antagonists (25, 36).

2. Antioxidants
As mentioned earlier, in addition to the direct mechanical trauma induced renal damage (due to the cavitation forces and shear stress), loss of renal capillary integrity resulting in tissue edema and subsequent ischemia and hypoxia have also been found to be responsible in SWL induced renal parenchymal alterations. Again, both local and regional vasoconstriction were also regarded as the contributing factor in the formation of tissue hypoxia and free radical formation. Following the ischemia induced renal tissue damage, studies again have indicated that the damaged cells in turn would produce an environment favourable for crystal retention and provide membranous debris that promotes crystal nucleation, aggregation and adherence. As a consequence of all these mechanisms, renal parenchymal ischemia resulting in free radical formation is now accepted as important causative factor not only for the induction of SWL related renal damage but also in promoting de novo calcium oxalate crystallization due to the damaged urothelium (47-53). Although free radical formation is a normal process of cellular metabolism (within normal limits of production), when produced in abnormal levels due to a variety of noxious stimuli including SWL (33), free radicals exhibit their toxicity by initiating the lipid peroxidation of cellular membranes. Therefore, limitation of free radical production, regardless of its predisposing origin, would be a therapeutic intervention both to prevent renal damage and stone formation/regrowth in individuals at risk. A variety of agents (majority of which are antioxidant in nature) have been used in an attempt to limit either HESW induced renal tubular damage or possible stone recurrence.

Citrate
Citrate is a well-known potent inhibitor of renal stone formation and it has been used as a free radical scavenger in a variety of experimental and clinical studies. In this regard, citrate based medications have been applied during the peri-operative period of shock wave lithotripsy, not only to inhibit stone formation and facilitate fragment passage, but also to reduce the incidence of shock wave induced renal damage. In their original study, Cicerello et al., has demonstrated its inhibitory action on new stone formation and contribution for the passage of residual fragments following SWL (34). In addition to the inhibition of heterogeneous nucleation and solubilization of calcium salts, the action of citrate may be further enhanced by the protective effect on the urothelium. This direct tissue effect may not only inhibit stone formation due to free radical production, but also protect the renal parenchyma from shock wave induced free radical injury. In an in vivo model, Delvecchio et al. have demonstrated that the free radical surge induced by SWL can effectively be blocked by the use of free radical scavengers, such as allopurinol (55). They evaluated the potential beneficial effects of citrate, as both a medication to inhibit new stone formation, as well as a scavenger of free radicals. Their results suggested that the use of citrate, as well as a documented free radical scavenger, vitamin E, significantly reduces the free radical surge induced by shock waves in an in vitro MDCK cell culture model (55). On the other hand again, Tungsanga and co-workers suggested that although potassium citrate treatment might prevent stone formation by increasing urinary citrate excretion, its effects on parameters of oxidative stress and tubular damage were uncertain. In their study, the drug...
caused the reduction of radical-mediated reactions in plasma and erythrocytes, as seen from the decrease in P-MDA and E-MDA, and the increase in plasma vitamin E (57). Huang et al. also reported the decrease of free-radical generation after the treatment of urolithic rats with vitamin E and potassium citrate. Therefore, the significant increase of vitamin E after treatment was due to an indirect effect of potassium citrate in reducing reactive oxidants (57).

Related with this subject again, potassium citrate demonstrated acceptable success rates with respect to stone regrowth (58-60). In vitro studies showed that citrate inhibits calcium oxalate crystal growth on kidney stone fragments and citrate therapy has gained increasing attention in the prevention of relapses in metabolically active stone disease. Potassium citrate complexes with urinary calcium and is a direct inhibitor of calcium oxalate crystallization. After a 3-year follow-up Tekin et al. were able to demonstrate that the proportion of the patients remaining stone-free on K-citrate was 72% while the corresponding value for untreated control patients was 20%. The stone formation reduced from 1.2 to 0.1 respectively (62). In one of our previous study again, potassium citrate has been found to reduce new stone formation in pediatric cases after SWL to a lesser extent (63).

Allopurinol

As a potent antioxidant agent, although the exact underlying mechanism has not been fully outlined, allopurinol was found to ameliorate the side effects of shockwave lithotripsy (19). It has been shown that patients under allopurinol medication showed a lower excretion of 2-microglobulin and albumin and a greater excretion of Tamm-Horsfall protein (64). Taking the HESW induced free radical formation and altered cell membrane permeability into account, it is likely that allopurinol could protect renal tubular cells by inhibiting xanthine oxidase and limiting free radical production which ultimately results in a decrease in cell permeability after SWE. Although direct evidence in SWE is lacking, oxygen radicals are likely to play a key role in perpetuating ischemia-induced cell damage by increasing cell permeability (64).

Lastly, by keeping the resting [Ca++] approximately 50% lower in HESW treated cells than non-treated cells, allopurinol might protect the kidney cells against SWL-induced damage through this mechanism and, in turn, may attenuate the severity of side effects that patients suffer from SWL (65).

Vitamin E

Vitamin E is the major lipid soluble antioxidant present in the cell membranes and acts synergistically with the other antioxidants. It can react with oxidant radicals forming mainly in ischemic conditions and stop the process of lipid peroxidation. As a very potent antioxidant, vitamin E appears to be an effective scavenger, especially in preventing the deleterious effects of free radicals in parenchymateous organs (16, 17, 65, 66, 67). It has been shown that a deficiency of vitamin E, which protects well against free radical formation, leads to parenchymateous organ damage, for example in testes or kidneys. Results of some studies have suggested that the use of citrate, and as a documented free radical scavenger, vitamin E, significantly reduces the free radical surge induced by shock waves in an in vitro MDCK cell culture model (65).

Again, restoration of antioxidant enzymes (glutathione peroxidase and catalase) towards the control level, inhibition of free radical production and resultant lipid peroxidation are the main possible protective mechanisms induced by Vitamin E which donates a hydrogen atom to the chain propagating lipid peroxy radicals; giving rise to phenoxy radicals of the antioxidants (68). Last but not least studies have shown that the effective antioxidant potency of vitamin E might be due to its higher recycling efficiency of short hydrocarbon chains (69-73).

Selenium

Selenium is normally incorporated in glutathione peroxidase (GPx), an enzyme that is crucial for oxygen-derived free radical homeostasis and again vital for the protection of the cells against lipid peroxidation by catalyzing the reduction of hydroxyl radicals (74). A further protective mechanism of selenium is the direct reduction of lipid hydroperoxides of the cell membrane. Several studies also demonstrated the protective effect of selenium against free radical-induced tissue damage (e.g., heart, liver, endothelial cells) (74, 75) in vivo. Selenium has also been shown to reduce the renal tubular toxicity of cis-platinum which is also caused by the increased formation of reactive oxygen species (75). Since these mechanisms are important for shock wave-induced renal tubular damage, the limitation of shock wave-induced cellular injury by selenium, as observed in cultured MDCK cells and in rats, is probably due to the increased activity of glutathione peroxidase. By protecting the cell membranes and the mitochondria, the shock wave-induced leakage of intracellular and membrane enzymes could be reduced.

In summary, selenium, a well-known free radical scavenger, in the light of the fact that free radical formation is an important mechanism in shock wave induced renal tubular damage, may be used in clinical conditions to ameliorate the shock wave-induced tubular impairment (76, 77). However, further experimental and clinical studies are needed to establish its protective role on this aspect.

Other agents

In addition to the above mentioned and partly established agents, some other agents including angiotensin II blockers, green tea, nitric oxide, astragalosides have also been used in an attempt to prevent or limit the shockwave-induced oxidative stress and subsequent tubular changes. Although the studies did demonstrate the potential protective effects of these agents to some extent, it is clear that further experimental and clinical studies are certainly needed to outline their possible role on HESW induced renal parenchymal changes (77-83).

Conclusions

Experimental as well as clinical findings reported in the literature suggest that treatment with SWL causes renal...
parenchymal damage mainly by generating free radicals through ischaemia/reperfusion injury mechanism. Although SWL-induced renal damage is well tolerated in the majority of healthy cases with no permanent functional and/or morphologic side effects, a subset of patients with certain risk factors requires close attention on this aspect among which the ones with pre-existing renal disorders, urinary tract infection, previous lithotripsy history and solitary kidneys could be mentioned.

It is clear that in such patients lowering the number of shock waves (per session) could be beneficial and has been applied by the physicians as the first practical step of diminishing SWL induced parenchymal damage. On the other hand, taking the injurious effects of HESW induced free radical formation on renal parenchyma and subsequent histopathologic alterations into account, physicians searched for some protective agents in an attempt to prevent or at least to limit the extent of the functional as well as the morphologic alterations. Among these agents calcium channel blocking agents (verapamil and nifedipine), antioxidant agents (allopurinol, vitamin E and selenium) and potassium citrate have been used to minimize these underestimated adverse effects. Additionally, therapeutic application of these agents on reducing stone recurrence particularly after SWL will gain more importance in the future in order to limit new stone formation in these cases. Lastly, as experimental and clinical studies have demonstrated, combination of anti-oxidants with free radical scavengers may provide superior renal protection against shockwave induced trauma.

However, we believe that further investigations are certainly needed to determine the dose-response relationship between the damaging effects of ESWL application and the protective role of these agents.

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INTRODUCTION
The treatment of renal calculi was revolutionised with
the introduction of shock wave lithotripsy (SWL) nearly
30 years ago (1). In fact SWL quickly became the treat-
ment of choice for most upper urinary calculi. However,
as our approach to the treatment of urinary calculi has
changed, so has our concept of what constitutes success-
ful treatment. During the era of open stone surgery the
presence of residual fragments suggested a failed proce-
dure, even if those remaining fragments were small (2).
Nowadays patients with small fragments after SWL are
often considered successfully treated, based on an
assumption that these residual fragments have little clin-
ical significance.
Unlike more invasive urologic treatments, SWL does not
remove stones; it disintegrates them producing residual
stone material, which must be passively excreted. A sig-
nificant number of patients, however, do not completely
expel all stone material despite adequate fragmentation
and these patients are found to have small residual frag-
ments in post-SWL follow-up studies.
Asymptomatic fragments smaller than 5 mm and with-
out associated infection or obstruction were defined Clinically Insignificant Residual Fragments (CIRF),
although it has been reported that many grow, becoming
symptomatic or requiring intervention (3).
This article reviews the implications of residual frag-
ments after lithotripsy and suggests guidelines for their
management.

INCIDENCE OF RESIDUAL FRAGMENTS
Only a small percentage of patients are immediately
stone free after SWL treatment. There is radiological evi-
dence of residual stones in 85% of patients when dis-
charged from the hospital (4). The majority of these frag-
mants will be passed within a few weeks. With increas-
ing renal persistence of residual fragments the probabili-
ty of stone clearance seems to decrease (5).
In the absence of symptoms, most Stone Centres recom-
end radiographic evaluation approximately one month
after SWL and at varying intervals thereafter as deemed
clinically necessary. Such follow-up studies show that
residual fragments are still present in 24% to 36% of the
cases 3 months after SWL (6-9).
Several factors affect the presence of residual fragments.
They include stone composition, size, and location, as
well as anatomy of the urinary tract. Hard stones (e.g.
cystine, brushite or calcium oxalate monohydrate) are
less likely to be cleared completely after SWL and more
likely associated with residual fragments (10-12).
Previous studies showed that pre-SWL stone-burden and
the presence of multiple stones increase the incidence of
residual fragments dramatically (13-15). The clearance
of fragments is, moreover, delayed for lower pole renal
calculi and if certain spatial anatomic factors, such as the
infundibulopelvic angle, infundibular length and
infundibular width, have an impact (16, 17). However, a
recent study has reported that lower pole anatomy has
not significant influence on clearance of fragments after

Residual fragments after shock wave lithotripsy (SWL) represent a common and still
controversial problem. These fragments can be important risk factors for stone growth
and recurrence, may lead to symptomatic events and need further urologic treatment.
The term “Clinically Insignificant Residual Fragments” (CIRF) is therefore a mis-
nomer and should be abandoned.
Although the goal of urolithiasis treatment is stone-free status, that the presence or non-infect-
ed, non-obstructive, asymptomatic residual fragments after SWL should be managed metabol-
ically in order to prevent stone growth and recurrence.
Further urologic treatment is warranted if the clinical indications for stone removal are present.

KEY WORDS: Clinically Insignificant Residual Fragments (CIRF); Shock Wave Lithotripsy (SWL).

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Furthermore SWL should not be considered in cases in which anatomic abnormalities of the urinary tract may preclude the passage and elimination of adequately fragmented stones: ureteropelvic junction substenosis, ureteral obstruction, calyceal diverticulum, stones in proximity to large adjacent renal cysts, presence renal anomalies (e.g. horseshoe or malrotated kidneys) or transplanted kidneys (15, 19) (Figure 1). The incidence of residual fragments depends on the imaging modality used to identify them. Although the presence of residual fragments is usually reported as a function of the findings on plain abdominal radiographs, plain films have significant limitations. Densted et al. showed that, compared with direct endoscopic visualization, 35% of residual fragments are missed on plain radiographs (20). Jewett et al. subsequently studied the interobserver and intraobserver variability in assessing the presence of post SWL residual fragments with plain films (21). Given the limitations of plain films, the true incidence of residual stones is therefore probably higher than generally reported. As such, at least some of the reported post SWL recurrences represent growth of missed or non-radiologically visible residual fragments. More sensitive radiographic modalities recently available, such as noncontrast spiral CT, have proved superior to plain radiography; linear tomography and ultrasound in detecting post procedural residual stones (22-24).

**Fate of residual fragments**

Residual fragments may be important for a variety of reasons: they may act as a nidus for recurrent stone growth, they can become acutely dislodged and cause significant obstruction with pain and infection, or they may be the source of persistent infection. After stone fragmentation, the underlying metabolic abnormalities for recurrent stone formation persist. Supersaturation of the urine with stone-forming salts or lack of stone inhibitors may accelerate the growth of residual fragments and promote new stone recurrence. Several groups have reported stone recurrence from such fragments in varying percentages (3, 5, 8, 25-29) (Table 1). Buchholz et al. (27) reported a very low 2% regrowth rate of residual fragments at a mean follow-up of 2.5 years (27), while a far higher 59% regrowth rate at a follow-up of 15 months was published by Kaithan et al. (25).

Carr et al. reported that patients rendered stone free after SWL demonstrate a higher stone-recurrence rate than a similar group of patients treated by percutaneous nephrolithotomy with ultrasonic fragmentation (30). The higher recurrences after SWL may be caused by microscopic sand particles migrating to dependent calyces and acting as nidi for new stone formation. By dramatically increasing the surface area of the original stone, SWL may favor new stone growth through heterogeneous nucleation and crystal aggregation by exposing the stone area to a lithogenic environment.

A prospective study followed 160 patients with 4 mm or smaller asymptomatic calcium oxalate or calcium phosphate stone fragments after SWL for a mean of 23 months. Overall the fragment regrowth rate was 18.1%, while 41.9% of fragments remained unchanged in size during
long-term follow-up. At the end of follow-up 36% had passed and the majority did so within the first year after SWL. Using Kaplan-Meier estimates, the probabilities of fragments passing, decreasing in number or remaining stable was 80% over 5 years. At follow-up, however, 43.1% of these patients had developed significant symptomatic episodes that needed intervention when stones migrated to the ureter or increased in size (3).

Historically infection stones have required aggressive extirpative management. The urea-splitting bacteria necessary for the formation of these stones may persist in the residual fragments, thus promoting a cycle of persistent infection and accelerated growth (31). Sterilisation of residual infection stones is the goal standard of the treatment. While the role of long-term antibiotics or urease inhibitors in this setting is unproven, we have noted at 12 months follow-up the effectiveness of prophylactic antibiotics not only on clearance, but also on the growth and aggregation of residual infection fragments after SWL (32).

**Management of residual fragments**

The management of residual fragments is controversial, especially given the potential for these fragments to grow and become clinically significant.

With the goal of improving stone-free rate, several Authors have advocated early retreatment. Kring et al. retreated patients who showed residual fragments 2 months after SWL and 60% of these patients were subsequently rendered stone-free (33). Moon and Kim applied an additional session of SWL to small (3-4 mm) residual fragments present 1 month after SWL and achieved a 92% stone-free rate at 6 months (34). Although repeat SWL may aid clearance of residual fragments, it is unclear which patients benefit most from retreatment. Clearly these fragments will pass spontaneously or remain unchanged in a significant number of patients. Furthermore, although the complication rate of SWL is minimal, patients are inconvenience and workdays are lost.

Nowadays the cost of medical procedures must be considered. Secondary treatment could be considered in asymptomatic, obstructive residual stones or in stone-associated urinary tract infection. Treatment could also be considered for asymptomatic residual stones in patients who cannot risk an episode of kidney colic (e.g. airplane pilots) or urinary tract infection (e.g. transplant patients) (3, 35).

In patients with non-obstructive, non-infectious, asymptomatic residual fragments, one might consider aggressive medical therapy with the correction of underlying metabolic disorders to prevent stone growth or formation of new calculi. One or more metabolic abnormalities can be identified in up to 77% of stone-forming patients (36, 37). Several studies endorse the role of medical treatment after SWL, especially when residual fragments are present. Fine et al. evaluated 80 patients who underwent a full metabolic evaluation after SWL and were given selective medical therapy (38). Specific attention was paid to the significance of residual stone fragments and their effect on stone growth or recurrent stone formation during long-term follow-up. In patients with residual fragments after SWL, specific medical therapy produced an 81% stone free rate. More than half of the patients with residual stone fragments who were not managed with medical therapy showed significant stone growth at follow up. Only 16% of the similar group of patients on medical treatment demonstrated increase in stone size.

Our randomized prospective trial studied the effects of citrate therapy or conservative measures (dietary limitation of dairy products and salty foods and increased fluids) on residual fragments 6 to 8 weeks after SWL (39). At a follow-up of 12 months there was 75% reduction in the clearance of calcium stone fragments in patients receiving citrate treatment. Only 32% of the patients following conservative measures, however, had clearance of their calcium stone fragments. Similarly, in patients with residual infected fragments, non selective medical therapy with citrate cleared residual fragments in 86% of the patients, whereas only 40% of the patients following conservative measures had clearance of their infected fragments.

Another study evaluated the effect of potassium citrate on residual stone fragments after SWL for lower pole calcium oxalate urolithiasis (40). Four weeks after SWL 34 patients who had residual stones were randomly assigned to a citrate therapy or control group (high fluid intake recommended to achieve a minimum daily urine output of 2 l and avoidance of dietary excesses). At the 12-month follow-up 44.4% of the treated patients were stone free, whereas clearance was obtained in only 12.5% of the control group.

A recent randomized study confirms the effectiveness of potassium citrate in children with residual calcium fragments 4 weeks after SWL (41). Specific attention was paid to the significance of residual stone fragments and their effect on stone growth or recurrence in the treated and the control group (no specific preventive measure). At 24.4 months of follow-up, children who had received citrate treatment showed acceptable regrowth and recurrence rates (18.1%), whereas both recurrence and regrowth were evident in most children of the control group (72.7%).

**Table 1.**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Follow-up (months)</th>
<th>Growth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanetti et al. 1991</td>
<td>56</td>
<td>25.8</td>
</tr>
<tr>
<td>Nakamoto et al. 1993</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>Streeam et al. 1996</td>
<td>89</td>
<td>18.1</td>
</tr>
<tr>
<td>Zanetti et al. 1997</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Bucholz et al. 1997</td>
<td>30</td>
<td>2.1</td>
</tr>
<tr>
<td>Khaitan et al. 2001</td>
<td>15</td>
<td>59</td>
</tr>
<tr>
<td>Osman et al. 2005</td>
<td>60</td>
<td>21.4</td>
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</tbody>
</table>
CONCLUSIONS
These data suggest that residual stone fragments after SWL pose a significant risk for stone growth or recurrent stone formation. Medical treatment improves the outcome of residual fragments by decreasing growth or agglomeration in patients in whom clearance was not achieved. More importantly, such therapy may be allowing spontaneous passage, thus increasing the clearance rate.

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CASE REPORT

Recurrent renal colic in young people: Abdominal Munchausen syndrome - a diagnosis not to forget.

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Summary

The Munchausen’s syndrome (MHS) is a rare psychiatric disorder classified among the self-manipulated diseases. Incidence of Munchausen syndrome peaks in young-to-middle-aged adults, but it has been reported in patients of all ages (ie, childhood through advanced age). Diagnosing Munchausen syndrome is very difficult, but early diagnosis could to a considerable extent prevent the iatrogenic risks. Indeed, the management of Munchausen syndrome is aggravated by the low compliance in these patients. We report an unusual case of MHS in urological practice, in order to demonstrate that the MHS is an underestimated and laborious to diagnose syndrome.

A 25-year-old single female affected by recurrent episodes of renal colic was admitted to our institution, reporting right acute flank pain and at least two previous periods of hospitalization due to bilateral acute flank pain with no evidence of urinary calculi or either morphological or functional alterations. Neither the urodynamic study nor abdominal CT scan nor pelvic NMR revealed any morphological or functional alterations. In order to exclude a multiple sclerosis, an encephalic NMR and neurological evaluation were also performed. At this stage, suspicion was raised regarding the possible factitious nature of her problem and a psychiatric consultation was made. On the basis of psychiatric consultation and the symptoms resolution with simple intravenous saline solution infusions, the diagnosis of factious illness (Munchausen syndrome) was confirmed. In the present case report, we stress the fact that the MHS is an underestimated medical problem and the necessity to evaluate the possible role of psychiatric disorders in the absence of pathological findings.

KEY WORDS: Factitious disorders; Malingering; Munchausen syndrome; Kidney; Somatization.

INTRODUCTION

The Munchausen’s syndrome (MHS) is a rare psychiatric disorder classified among the self-manipulated diseases but frequently unrecognized as such (1). It is due to either self-inflicted injury or imaginary symptoms of physical or mental illness, in order to receive medical care and hospitalization. The incidence of MHS is less than 10% of all factitious disorders observed in hospitalized patients (2). This syndrome is characterized by a triad of features: a) simulated or manipulated illness; b) pathological inventions of clinical identities including false names or biographies, and an inclination towards deception; c) wandering from place to place among different hospitals and antisocial behaviour (3). During hospitalization, the MHS patient is used to deceiving doctors and nursing staff in order to attract their attention or obtain medical treatment. This kind of patient prefers surgical departments due to a long diagnosis period before surgery (4). Failure to take this syndrome into account in everyday urological diagnostic practice can delay and make correct treatment difficult after repeated hospitalisations, examinations and often aggressive treatment (1), with a consequent patient quality of life worsening and increased hospitalization costs (4). We report an unusual case of MHS in urological practice, in order to demonstrate that the MHS is an underestimated and laborious to diagnose syndrome.

CASE REPORT

A 25-year-old single female (unemployed) affected by thalassemia minor and recurrent episodes of renal colic was admitted to our institution in January 2004. On
admission, she had right acute flank pain and she mentioned at least two previous periods of hospitalization in other urologic departments due to bilateral acute flank pain with no evidence of urinary calculi or either morphological or functional alterations. She denied a history of fever, trauma or other symptoms, except recurrent urethral pain and burning during voiding, with no evidence of microbiological demonstrated urinary infections.

The patient’s father is a factory worker and her mother is, nowadays, unemployed. She has two sisters and two brothers. She is the third in line. Physical examination at the admission time, revealed an intelligent young female, afebrile, with normal pulse and pressure. The Giordano’s sign was negative. The abdominal examination was normal. Urinary tract ultrasound, retrograde pyelography and ureteronephroscopy were performed without showing evidence of disease. Urinalysis did not present any abnormal results. The patient was discharged from our department after three days with a temporary oral non-steroidal analgesic therapy.

In October 2004, she was admitted to our institution again for a persistent bilateral flank pain. Urinary tract ultrasound, abdominal CT scan and bilateral retrograde pyelography were all negative. A gynaecological consultation excluded the relationship between the bilateral flank pain and evidence of an ovarian cyst, diagnosed at transvaginal ultrasound examination. After a few days of hospitalization, the patient presented an acute urinary retention of uncertain origin with acute pelvic pain and fever (around 38°C). Neither the urodynamic study nor pelvic NMR revealed any morphological or functional alterations. The patient continued to mention shudders and fever with recurrent episodes of bilateral renal colic, notwithstanding antibotics and non-steroidal analgesic compound sub-continual administration. To exclude a multiple sclerosis, an encephalic NMR and neurological evaluation were performed. At this stage, suspicion was raised regarding the possible factitious nature of her problem because of an inability to explain the cause of her fever and urinary symptoms. The appearance of fever peaks was continuously recorded when the patient was unattended by her relatives or nurses, and the analgesic administration was successfully substituted by simple intravenous saline solution infusions. A psychiatric consultation was made after counselling the patient without giving her a mention about suspected factitious disorder.

On the base of psychiatric consultation, the patient looks to be very defensive and suspicious about clinician’s questions. However, even if she described more accurately her urinary symptoms like a textbook presentation, many vagueness or inconsistency in the details of her medical problems were reported. In addition, she seemed to be under a great amount of stress. In the psychiatrist’s view, the patient may benefit from a long-term psychotherapy, without any change of improvement and, however, with a poor prognosis.

On the basis of psychiatric consultation and the symptoms resolution with simple intravenous saline solution infusions, the diagnosis of factious illness (Munchausen syndrome) was confirmed. The diagnosis of MHS was then discussed with the patient. She denied possible imaginary evidence of symptoms and left the hospital against medical advice immediately. The patient was lost to follow-up.

**DISCUSSION**

The MHS is a special type of factious illness, according to DSM-IV, with predominantly physical signs and symp-

<table>
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<th>MHS* Type</th>
<th>Author/Journal/Year of Publication</th>
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<td>Abdominal type</td>
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<td>Sharon S, MT Sinai J Med, 1974</td>
<td>1</td>
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<td>Jones WA, West J Med, 1978</td>
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<td>Ifundu O, NS Med, 1992</td>
<td>1</td>
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<td>Gordon R, Urology, 1993</td>
<td>3</td>
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<td></td>
<td>Schmidt F, Nephrol Dial Transplant, 1996</td>
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<td>Hemorrhagic type</td>
<td>Kerr DNS, Arch Int Med, 1980</td>
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<td>Orriols R, J Urol (Paris), 1981</td>
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<td>Eckhardt A, Urban &amp; Schwarzonberg, 1989</td>
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<td>Chew BH, Urology, 2002</td>
<td>2</td>
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<td>Neurological type</td>
<td>Heimbach D, Eur Urol, 1997</td>
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<td>Hermieu JF, La Presse Med, 2002</td>
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The table shows the Author, journal, year of publication and number of patients of each reported case of MHS in urological literature. MHS*: Munchausen Syndrome.
toms. Moreover, the MHS, like all factitious disorders, should be distinguished from malingering, in which the symptoms are produced intentionally but the subject has an obvious goal to achieve. Three types of MHS are distinguished in urological literature and they may occur in different combinations: a) the abdominal type: this is the most frequently observed, due to a wide range of possibilities for simulating abdominal pain; b) the hemorrhagic type: it presents artificially induced bleeding from the urethra or bladder; c) the neurological type: this is characterized by stimulation of fits or paralyses or sensory motor disorders (such as neurogenic bladder disorders) (5). Only twenty three cases of MHS are reported in the urological literature (Table 1). The present case report highlights two important findings to take into account in everyday urological practice: the MHS is an underestimated medical problem and the necessity to evaluate the possible role of psychiatric disorders in the absence of pathological findings. The necessity to reflect on the probable role of MHS in urological practice is also due to the fact that the prognosis of MHS patients is usually poor, due to both mental illness and medical treatment rejection by the patient (6). In addition, we would like to highlight that the support of a psychiatric consultation is need, particularly in order to plan a correct treatment protocol (4).

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References

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