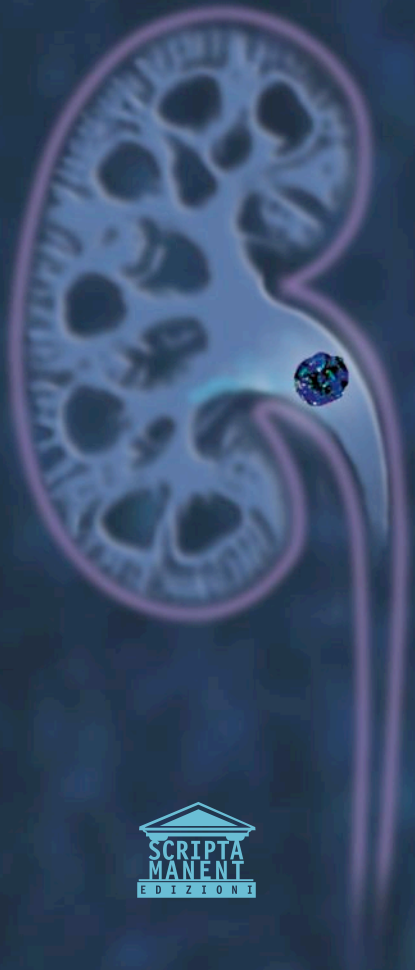
The Stone Handbook



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Contents

Preface

The stone disease is extremely diverse – from single stone formers with spontaneous stone passage to staghorn stones and stone diseases associated with severe metabolic abnormalities such as renal tubular acidosis and primary hyperoxaluria.

It is obvious that these different conditions should be dealt with selectively. In this context sharing knowledge on clinical practices – tips and tricks – between practising stone clinicians becomes especially important, and the most effective way that tips and tricks may be lifted up into an academic sphere is through international knowledge exchange.
It is with this respect that this handbook on stone management plays a particular important role by creating a platform for exchange of clinical expertise.

The contributors are international renowned stone experts, sharing with us their views of different approaches to the great variety of urinary stone diseases.

The handbook offers a unique synthesis of theory and tips-and tricks-technology, bridging basic science and daily clinical practice.

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Renal colic

1. Pathophysiology of renal colic

Ureteral obstruction by a stone induces massive dilatation of renal capsule, renal pelvis and the calyceal system. This is followed by hyperperistalsis of the ureter, i.e. the ureter tries to propagate the stone downwards to the bladder. Peristalsis is induced by so-called pacemaker cells (atypical smooth muscle cells) in the pelvic region [1].

The modulation of ureteral peristalsis is complex and incompletely understood [1]. It is a receptor-mediated process, whereby cholinergic (muscarinic), adrenergic and non-adrenergic/non-cholinergic receptors are involved. Among others, α-receptors (contraction), β-receptors (relaxation), prostaglandins (PG F2α: contraction, PG E_1/E_2: relaxation), histamin H_1-receptors (contraction), histamine H_2-receptors (relaxation) and serotonin (contraction) modulate ureteral peristalsis [1].

Hyperperistalsis of the ureter due to an obstructing stone induces the most intensive pain that human beings – with the exception of the pain of a woman during childbirth – may suffer from.

If ureteral obstruction persists for more than 1 day, obstructive uropathy occurs: rising intrarenal pressures induce local renal production of potent vasoconstrictive compounds which lower glomerular capillary pressure and thereby reduce glomerular filtration rate [2, 3].

2. Diagnostic work-up

2.1. Symptoms

In patients with acute colicky pain, various diagnostic measures have to be applied in order to exclude other causes of acute flank pain, mainly intraabdominal processes such as gall stone disease,

pancreatitis, diverticulitis, appendicitis, pyelo-nephritis or ruptured abdominal aortic aneurysm.

2.2. Laboratory investigation

Serum creatinine has to be checked due to the possibility of decreasing renal function with persisting ureteral obstruction. Elevated serum ionized calcium (or total calcium and albumin) may indicate hyperparathyroidism as a cause of stone formation.

Urine has to be tested be dipstick as well as microscopically for the following features:

- Urinary tract infection, i.e. pyelonephritis, has to be excluded.
- Of all patients presenting with the symptoms of acute renal colic, 90% exhibit micro- or macrohematuria [4]. On the other hand, only 14% of patients with ureteral colic do not present with hematuria (either dipstick or microscopy) [5].
- Measurement of urine pH is of utmost importance. Low urine pH (clearly below 5.5) indicates *"undue urine acidity"* and is often the cause of uric acid stone formation due to the low solubility of uric acid at lower pH values [6]. On the other hand, urine pH in the range of 6.2 to 7.5 may indicate a tubular acidification disorder (usually incomplete distal renal tubular acidosis) which is associated with calcium phosphate (apatite, brushite) stone formation [6].
- Microscopic crystalluria: the appearance of single crystals in the urinary sediment does not prove stone disease except for hexagonal cystine crystals which always indicate stone formation due to cystinuria. For many years, it has been known that large aggregates of calcium crystals are more common in recurrent stone formers than in non-stone formers [7].

2.3. Radiologic evaluation

Although ultrasonography is highly specific (greater than 90%) for detecting stones, its sensitivity is much lower and ranges from 11 to 24 percent [8]. It is therefore not to be used for a precise diagnosis of

"stone burden", i.e. number, sizes and locations of stones. However, it is well suited for detecting hydro-nephrosis and ureteral dilatation if ureteral obstruction has lasted at least 24 hours; before 24 hours of obstruction, dilatation of ureter and renal pelvic structures may be totally missed by ultrasound! Ultrasonography is an appropriate initial imaging test in patients with colics during pregnancy [8].

- Unenhanced helical CT is the best imaging study for diagnosing a renal/ureteral stone in a patient with acute flank pain; its sensitivity and specificity amount to 96 and 100 percent, respectively [8].
- If helical CT is not available, plain abdominal radiography should be performed, since up to 90 percent of calculi are radiopaque [8].
- Intravenous urography – previously the gold standard – is clearly less sensitive and less specific than helical CT [8] and is therefore no more used in settings where helical CT is available.

3. Treatment of renal colic

Due to the pathophysiologic complexity, it is not surprising that a huge variety of therapeutic modalities for treating renal colic has been applied in animal experiments as well as in the clinical setting. Subsequently, treatments with proven evidence in randomized clinical trials will be summarized.

3.1. Summary: suggested medical treatment of renal (ureteral) colic

No forced hydration, normal oral hydration !

Intravenous fluid administration only in case of protracted vomiting.

NSAID: mandatory (if not contraindicated)

Diclofenac 2 x 75 mg orally or i.m. / day

Ketorolac up to 3 x 30 mg i.v. / day + Alpha-blocker:

mandatory in distal, possible in proximal stones > 4 mm
e.g. Tamsulosin 400 mg 1 tabl. / day + corticosteroid (?)

Non-opioids

Paracetamol 1 g i.v. (max. 4 x / day)
Novaminsulfon (*Metamizol, Novalgin®*) 500-2000 mg i.v.

Opioids

Emergency Morphine 10 mg i.v. or Pethidine 25-50 mg i.v.
NO pethidine for regular (chronic) treatment
(opioid dependence) !
Ongoing colics (days) oral long-acting opioid preferred
(e.g. oxycodone/naloxone combination 10-40 mg every 12 h)

The following paragraphs provide detailed evidence from clinical trials for the proposed treatment regimen.

3.2. Analgesics

In the emergency situation, the main goal is to get the patient pain-free. In the few randomized trials that have been performed, paracetamol is surprisingly effective.

Intravenously administered paracetamol (1 g) had a analgesic effect that was equal to intravenous morphine i.v. (0.1 mg/kg BW) after 30 minutes of administration [9].

In comparison with the non-steroidal anti-inflammatory compound piroxicam (20 mg intramuscularly), paracetamol (1 g intravenously) was even superior with respect to its analgesic effect [10].

- Non-steroidal anti-inflammatory drugs (NSAIDs) are clinically highly effective in the treatment of acute colicky pain, most likely also because they reduce the local edema at the site of the obstructing calculus. In the absence of absolute/ relative contraindications (i.e. renal insufficiency, heart failure, uncontrolled hypertension, coronary heart disease, gastric ulcer), NSAIDs should always be administered in patients with acute renal colic. In a systematic review of 20 studies with 1613 patients by the *Cochrane Renal Group*, parenterally applied NSAIDs in comparison with opioids provided marginally better

analgesia than opioids, although both classes of drugs reduced pain significantly: on a 100 mm-visual analogue scale, pain intensity was on average 4.6 mm lower with NSAIDs, and patients receiving NSAIDs experienced less side effects than those receiving opioids [11].

- In most studies with opioids, parenterally administered pethidine has been used [12]. This compound has a very rapid onset of activity as well as a short duration of the analgesic effect. This carries a great risk of opioid dependence in predisposed individuals (genetic background, psychologic trauma in child-hood, history of dependence of other substances, family and occupational problems, social disintegration) [13].

  Already back in 1955, WHO hat issued a respective warning [12]. However, these problems with pethidine should not be generalized and used as a contraindication to all opioids, especially not to compounds in oral retarded forms for which to date no controlled studies are available.

- Novaminsulfon (*Metamizol, Dipyron*) has very good analgesic activity in patients with relal colic. In animal experiments, novaminsulfon exhibits spasmolytic effects in the obstructed/dilated ureter, which enhances analgesia [14]. In a comparative study in patients with extremely painful renal colics, intravenous novaminsulfon (2.5 g) was clearly superior to 100 mg tramadol and 20 mg butylscopolamin [15].

- Antimuscarinics: for many physicians, butylscopolamin (*Buscopan®*) still appears to be the first choice drug for treating renal colics. However, in the only placebo-controlled randomized study performed so far, butylscopolamin was not different from placebo in patients with renal colic receiving morphine and extra indomethacin, in that the required morphine doses were not different between groups [16]. This indicates a missing spasmolytic and thus analgesic effect of this antimuscarinic. Similar results were obtained in a further placebo-controlled study using another antimuscarinic agent [17].

3.3. Medical expulsive therapy–facilitating stone passage

Already theoretically, NSAIDs appear to be controversial compounds, since they inhibit the production of prostaglandin F_2 (ureteral contraction) as well as of prostaglandins E_1 and E_2 (ureteral relaxation). Therefore, it is of no surprise that, due to these contradictory effects, NSAIDs do not facilitate stone passage [18].

More recently, both alpha-blockers as well as calcium channel blockers have been demonstrated to dilate mainly the distal ureter and therefore to increase the probablity of spontaneous stone passage. A previous meta-analysis of 9 controlled studies in 693 patients with renal colic due to ureteral stones of 3.9 to 7.8 mm diameter found that stone passage rate was increased by 65% in patients receiving either additional nifedipine or β-blockers (mainly tamsulosin) *vs.* control patients receiving only NSAIDs, corticosteroids or diazepam [18]. A most recent Chinese study in more than 3000 patients with distal ureteral stones of 4-7 mm diameter, however, demonstrated a significant advantage of tamsulosin vs. nifedipine with regard to rate of stone passage after 4 weeks, duration of stone passage and need for additional doses of the NSAID diclofenac [19].
According to a small Turkish study, proximal ureteral stones up to 10 mm diameter pass more easily and within shorter time periods if patients are treated by tamsulosin in addition to analgesics; in addition, pain intensity of patients was reduced by 50% [20].

A most recent large meta-analysis reviewed 21 studies with predefined characteristics on tamsulosin and nifedipine between January 1980 and March 2010 [21]. Overall, patients on medical expulsive therapy (either nifedipine or tamsulosin) exhibited a significantly shorter stone expulsion time than patients on *"conventional"* treatment, i.e. 6.2 *vs.* 10.3 days [21]. However, the effect of nifedipine and tamsulosin was lost if stone size was below 5 mm [21]. Tamsulosin increased spontaneous stone expulsion rate and reduced expulsion time as well, whereas nifedipine only significantly affected stone expulsion rate, but did not alter expulsion time. Treatment discontinuation due to adverse effects appeared to occur more frequently with nifedipine [21].

- **In conclusion, alpha-blockers (especially tamsulosin) appear to have some advantages over calcium channel blockers (especially nifedipine) for facilitating passage of ureteral stones. They certainly have to given in distal (pre-vesical) ureteral stones and should be tried also in patients with proximal ureteral stones.**
- Some evidence against alpha-blockers: the first randomized and double-blind intervention study was performed in 90 patients with renal colics due to distal ureteral stones up to 7 mm diameter. All patients received diclofenac and – if needed – novaminsulfon; in addition, tamsulosin (0.4 mg/d) or placebo were administered [22]. After 21 days, the percentage if spontaneous stone passage (CT-controlled) was 86.7% with tamsulosin and 88.9% with placebo [22]. However, patients on tamsulosin had less pain and received a significantly lower number of analgesics than patients on placebo [22], which is clinically highly relevant.
- Corticosteroids: based on animal studies, mainly Italian Authors have favoured the use of corticosteroids against the local ureteral edema induced by an obstructing calculus [23]. In a prospective study in patients with distal ureteral stones of at least 5 mm diameter, spontaneous stone passage was not more frequent among patients receiving extra corticosteroids *vs.* those receiving only on demand-analgesics. Stone passage was significantly facilitated only in patients on both corticosteroids and the alpha-blocker tamsulosin [24].
- Therefore, corticosteroids appear to have a role as adjuvant therapy for facilitating stone passage in patients treated with tamsulosin (on possibly other alpha-blockers).

3.4. Forced hydration the *"mistaken expulsive therapy"*

Traditionally, patients with acute renal colic have been massively hydrated, because it was anticipated that an increased diuresis would

facilitate spontaneous stone passage. Already in theory, however, the attempt to propagate an obstructing and jammed ureteral calculus by massively rising urine flow and greatly enhancing intraureteral pressure appears counterproductive. Indeed, the elevated pressure proximally from the obstructing stone will increase the pressure in renal pelvis/calyces and thereby enhance pain.

- A systematic review of the *Cochrane Database* revealed that the issue of forced hydration had been investigated in just 1 prospective controlled study with 60 patients! The infusion of 3 liters over 3 hours in comparison to no parenteral fluid administration provided no benefit with respect to pain intensity as well as need for urological interventions or cystocopies [25].
- A more recent randomized trial confirmed these findings: besides conventional analgesic therapy, 43 patients with renal colic received an infusion, either 500 ml or 20 ml hourly [26].
  There were no differences between the 2 strategies with regard to pain intensity, required doses of morphine or rates of spontaneous stone passage[26].
- In addition, massive overhydration carries the risk for renal pelvic rupture with extravasation of urine and possibly infectious complications. Thus, forced hydration in patients with renal colic has no physiologiocal basis! As stated by *Foster MC, et al.* years ago [27], it is *"at least pointless and at worst dangerous."*
- Moreover, certain studies have even recommended antidiuresis in patients with ureteral colic by treating with the vasopressin analogue desmopressin [8].

In conclusion, patients with renal colic should be hydrated normally, and parenteral fluid administration should only be provided in cases of protracted vomiting due to renal colic.

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