Recent advances in management of ureteral calculi
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Abstract
The management of patients with urinary tract stone disease has changed dramatically over recent years, with current treatment modalities focused on their minimal invasiveness. In this article we will discuss the recent advances in the field of urolithiasis management, with a focus on medical expulsive therapy, extra-corporeal shockwave lithotripsy and ureteroscopy.

Introduction and context
Urinary tract stone disease is common; in Europe and in the USA the lifetime risk of developing a stone is between 5 and 12%, more often affecting men than women. The peak incidence is between the ages of 20 and 50 years. Unfortunately, within 5 years of their first bout of renal colic, 50% of patients will have stone recurrence. Not all renal tract calculi need active intervention as distal ureteric calculi of ≤5 mm in size have a spontaneous passage rate of 71-98%.

Stone size and location are important when considering conservative management, and analgesia is essential for such patients, as the passage of a calculus is associated with severe pain. Non-steroidal anti-inflammatory drugs are commonly used for this, however, patients placed on ‘watchful waiting’ may benefit from adjuvant treatment in the form of medical expulsive therapy (MET).

This article briefly reviews some of the current issues in the management of ureteric calculi, including MET, extra-corporeal shockwave lithotripsy and ureteroscopy. Some of the latest developments, including the use of isoproterenol and the application of robotics to flexible ureterorenoscopy, are also discussed.

Recent advances
Medical expulsive therapy
In recent years there has been a growing trend in administering medication (in addition to analgesia) to patients with distal ureteric calculi in order to help with expulsion of a calculus. There have been many trials demonstrating the efficacy of such an approach, highlighted below.

Alpha adrenoceptor antagonists
Tamsulosin, alfuzocin and terazocin have all been used in MET. The rationale behind the use of α₁-antagonists in MET has been that they are capable of decreasing the resting tone of the ureter and interfering with ureteric contractions, thereby decreasing the frequency of peristaltic contractions. Several studies have demonstrated that alpha blockers expedite stone passage, decrease pain, and hence, reduce analgesic requirements [1].

A recent study by Sigala et al. [2] looked at gene and protein expression of alpha adrenoceptors in the proximal, middle and distal ureters. They demonstrated that α₁d mRNA was the most common overall (and is expressed in all portions of the ureter), and that α₁ mRNA was found in greater abundance in the distal ureter than more proximally.

Tamsulosin has been the most commonly studied alpha blocker in MET and has equal affinity for α₁a and α₁d. Cervenákov et al. [3] were one of the first to carry out a double blind randomised trial using tamsulosin. In their series the rate of expulsion was 80.4% in the tamsulosin group versus 62.8% with standard therapy without tamsulosin. Since this study, the Italian authors
Dellabella and Porpiglia have been two key researchers in this field. Dellabella et al. [4] showed the effectiveness of tamsulosin in improving overall stone expulsion rates whilst reducing the patient’s analgesic requirements and risk of readmission to hospital, particularly when combined with a corticosteroid (which also reduced the time to expulsion). More recently, Porpiglia et al. [5] have reported the use of a second 10-day course of tamsulosin for patients who had not yet passed their stone after an initial treatment period of similar length. In this study, a further 80% of patients successfully passed a stone (compared with just under half of patients who passed them spontaneously without additional treatment). Figure 1 shows the effectiveness of alpha blocker MET in seven randomized controlled trials for distal ureteric stones.

Pedro et al. [6] performed a double blind randomised trial using alfuzosin. The alfuzosin group demonstrated a reduced time to distal stone expulsion and reduced analgesic requirements but the rate of expulsion was not increased. This may be an indication that alfuzosin is not as effective as the other alpha blockers.

Calcium channel blockers

The use of calcium channel antagonists such as nifedipine has also proved useful. Borghi et al. [7] carried out a double blind randomised trial involving 86 patients who received methylprednisolone with either placebo or nifedipine. The nifedipine cohort had a significantly higher rate of stone passage at 87 versus 65%. Other studies comparing nifedipine against tamsulosin seem to indicate that both drugs are useful, but tamsulosin is more efficacious [1,6].

Corticosteroids

Steroids have also been used to aid stone passage. The rationale for this treatment is that it reduces stone-induced oedema and hence allows a calculus to pass. Steroids combined with an alpha blocker proved more efficacious than either a steroid or alpha blocker alone. Porpiglia et al. [8] compared tamsulosin; deflazocort; a combination of tamsulosin and deflazocort; and analgesics (taken when required). The groups were comparable in terms of age, sex, and stone size and location. The rate of expulsion for the four groups was 60%, 37.5%, 84.8%, and 33.3%, respectively. Surprisingly, deflazocort on its own was not very efficacious compared to tamsulosin or combination therapy. Patients benefit greatly from combination therapy (84.8% expulsion rate) but if steroids are contraindicated (that is, because of diabetes or history of peptic ulceration) then adjuvant alpha blocker therapy will be of benefit (60% expulsion rate).

MET has been shown to be cost-effective by reducing the number of ureteroscopic procedures that would be required following observation alone. Provided that ureteroscopy is not extremely cheap and MET is not very expensive, or spontaneous stone passage rates are not extremely high (and therefore need neither MET nor ureteroscopy) or extremely low (and therefore require a ureteroscopy whether treated by MET or not), MET is a cost-effective treatment. In the USA, this approach would result in a theoretical $1,132 cost saving per patient over observation, a saving that is related to the very high cost of ureteroscopy in the USA and the relatively low cost of tamsulosin. In fact, due to the cost differences between the two treatments, if only one ureteroscopy per 100 treated patients is avoided because of MET, then it would still be a cost effective treatment in the USA [9].

Extra-corporeal shockwave lithotripsy

Extra-corporeal shockwave lithotripsy has been used for many years and is an effective treatment modality for a select group of patients. It has been shown to be very efficacious for upper ureteric stones of ≤10 mm in size. Multiple large series have shown stone-free rates of over 80% for proximal ureteral calculi. In a series of 397 patients with an upper ureteric stone, 91% had a calculus diameter of ≤14 mm and this cohort had an 84.3% stone-free rate at 3 months. However, with increasing
stone diameter the success rate decreases. For the Dornier Compact Delta lithotripter the success rate at 3 months was reported as 96% for calculi ≤10 mm and 90% for those 11-20 mm in diameter [10].

**Ureteroscopy**

Along with ongoing development of safety/working wires and basket design and size, one of the key advances in ureteroscopy relates to the improved image quality itself, with the development of digital ureteroscopes with ‘chip in the tip’ technology. Such systems can be illuminated by LEDs (light-emitting diodes) in the tip of the scope, and an external light source may not therefore be required. In addition to the remarkable improvement in image quality, such scopes are lighter (there is no need for an external camera to be attached), inherently safer (there is no risk of drape or patient burns from the external light source), and possibly more durable (there are no fragile fibre-optics within the scope since the image is transmitted digitally) [11,12].

It has been suggested that the considerable improvement in image quality over conventional analogue scopes may allow the earliest stages of stone formation to be better appreciated, and hence improve our understanding of the pathogenesis of calcium oxalate stone formation [13].

**Isoproterenol and ureteroscopy**

Through its effect on relaxation of ureteric tone, the use of endoluminal isoproterenol in the irrigation fluid has been shown to reduce pelvic pressure compared with saline irrigation without affecting heart rate or mean arterial blood pressure. Significant increases in intrarenal pressure do occur during ureteroscopy (especially during injection of contrast) and these may be associated with complications, including urinary sepsis due to pyelovenous and pyelolymphatic reflux. The reduction of intra-pelvic pressure, without associated cardiovascular side effects, therefore offers a potentially useful safety step in ureteroscopy [14].

**Robotics**

Whilst not reported for the treatment of ureteric calculi as yet, the extension of robotics to ureteroscopy deserves a mention. Desai and colleagues [15] have recently described the use of a modified robotic catheter system for ureterorenoscopy that had been originally developed for intra-cardiac applications.

In this feasibility study using a pig model, they were able to inspect 98% of calyces using a steerable guide catheter controlled remotely via a three-dimensional joystick. They reported that the robotic method was ‘stable, easily manoeuvrable, and ergonomically superior’ to conventional ureterorenoscopy. Intra-renal therapeutic manoeuvres were also possible, including the complete fragmentation of small stones. They found that the combination of the precise positioning of the catheter tip and its subsequent stability allowed the system to be ‘parked’ in a calyx for prolonged periods, improving the ability to target small fragments for further fragmentation. However, they identified significant extravasation of irrigation fluid following these procedures, and have subsequently reduced the size of the prototype ureterorenoscope to 7.5 F [15].

**Implications for clinical practice**

Although already in widespread use, and supported by the 65% relative increased chance of stone passage compared with non-treatment, MET still requires a well-designed randomized trial to confirm its effectiveness and best practice in the management of ureteric stones. Until then, MET is useful in patients who do not require more urgent intervention, but its ‘off-label’ use should be emphasized.

The ability to treat large, proximal ureteric stones, with a good chance of being stone-free in one procedure, continues to be the goal of ureteroscopic stone management. The use of isoproterenol, the first report of pharmacological manipulation of the ureter intra-operatively [14], could potentially reduce the risk of septic complications following ureteroscopy; if so, then it may not be long before this strategy is taken up by others, and, if proven to be effective in randomized trials in humans, could become as standard a step in ureteroscopy as the insertion of a safety wire.

Using their robotic system, Desai *et al.* [15] were able to decrease the time required for a complete examination of the kidney down to under a minute; however, the learning curve for this is likely to be greater for those without as much robotic or ureterorenoscopic experience. Further improvements to the method, and details of its use in a clinical setting, will no doubt reach the literature soon, and evidence of wider dissemination of this technique is pending. Inevitably, the cost implications of establishing a robotic ureterorenoscopic programme, relative to the ability of experienced operators to gain access to each calyx, and similarly to ‘park’ the tip of a conventional flexible ureterorenoscope in the desired calyx for sufficient time to completely treat the stone within, remains to be quantified and will play a significant role in wider acceptance.

**Abbreviations**

MET, medical expulsive therapy.
Competing interests
The authors declare that they have no competing interests.

References
1. Lipkin M, Shah O: The use of alpha-blockers for the treatment of nephrolithiasis. Rev Urol 2006, 8(Suppl 4): 4S35-42.
2. Sigala S, Dellabella M, Milanesi G, Fornari S, Faccoli S, Palazzolo F, Peroni A, Mirabella G, Cunico SC, Spano P, Muzzonigro G: Evidence for the presence of alpha 1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn 2005, 24:142-8.
3. Cervenákov I, Fillo J, Mardiak J, Köpencý M, Smirala J, Lepies P: Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker - tamsulosin. Int Urol Nephrol 2002, 34:25-9.
4. Dellabella M, Milanesi G, Muzzonigro G: Medical-expulsive therapy for distal ureterolithiasis: randomized prospective study on role of corticosteroids used in combination with tamsulosin-simplified treatment regimen and health-related quality of life. Urology 2005, 66:712-5.
5. Porpiglia F, Fiori C, Ghignone G, Vaccino D, Billia M, Morra I, Ragni F, Scarpa RM: A second cycle of tamsulosin in patients with distal ureteric stones: a prospective randomized trial. BJU Int 2009, 103:1700-3.
6. Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M: Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J Urol 2008, 179:2244-7.
7. Borghi L, Meschi T, Amato F, Novarini A, Giannini A, Quarantelli C, Mineo F: Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. J Urol 1994, 152:1095-8.
8. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, Scoffone C, Terrone C, Scarpa RM: Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? Eur Urol 2006, 50:339-44.
9. Bensalah K, Pearle M, Lotan Y: Cost-effectiveness of medical expulsive therapy using alpha-blockers for the treatment of distal ureteral stones. Eur Urol 2008, 53:411-8.
10. Kiyakai K, Halebian GE, Preminger GM, de la Rosette J: Shock wave lithotripsy or ureteroscopy for the management of proximal ureteral calculi: an old discussion revisited. J Urol 2007, 178:1157-63.
11. Mitchell S, Havranek E, Patel A: First digital flexible ureterorenoscopy: initial experience. J Endoural 2008, 22:47-50.
12. Andonian S, Okeke Z, Smith AD: Digital ureteroscopy: the next step. J Endoural 2008, 22:603-6.
13. Humphreys MR, Miller NL, Williams JC Jr, Evan AP, Munch LC, Lingeman JE: A new world revealed: early experience with digital ureteroscopy. J Urol 2008, 179:970-5.
14. Jung H, Narby B, Frimodt-Møller PC, Osterh Pj: Endoluminal isoproterenol irrigation decreases renal pelvic pressure during flexible ureterorenoscopy: a clinical randomized, controlled study. Eur Urol 2008, 54:1404-13.
15. Desai MM, Aron M, Gill IS, Pascal-Haber G, Ukimura O, Kaouk JH, Stahler G, Barbagli F, Carlson C, Moll F: Flexible robotic retrograde renoscopy: description of novel robotic device and preliminary laboratory experience. Urology 2008, 72:42-6.
16. Hollingsworth JM, Rogers MA, Kaufman SR, Bradford TJ, Saint S, Wei JT, Hollenbeck BK: Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet 2006, 368:1717-9.