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IS THERE AN IDEAL TREATMENT FOR THE ACUTE RENAL COLIC?

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1. INTRODUCTION

Urolithiasis and renal colics are very common around the world. In fact, we´ve often seen this suffering among family members, friends or close acquaintances and all of them used similar words to describe its pain: a severe, unbearable or excruciating pain in the flank. Every time I was consulted, I found myself unable to specify which medical treatment stands out from the rest at fighting against the acute renal colic.

So honestly, a bit of ignorance and a lot of curiosity about fairly demonstrated data on the treatment of the acute renal colic is what encouraged me to research on this subject for my end-of-career project. Through the shaping of the project, other important matters came along, such as the economic impact of this illness or the standard procedures for its diagnosis. In the following lines, I´ll present what I consider the highlights about the renal colic, in other words, what I consider everyone must have in mind, fresh-baked, before diving further into this project.

1.1. DEFINITION & PHYSIOPATHOLOGY:

Renal calculi consist of crystal aggregates that deposit in the collecting ducts. Urinary stones arise because of the breakdown of a delicate balance between two opposing conditions: solubility and precipitation of salts, as kidneys must conserve water, but must excrete materials that have low solubility (1, 2). Additionally, urine contains substances such as citrate, pyrophosphate and glycoproteins that act as a protective mechanism, inhibiting crystallization. However, when urine becomes supersaturated with insoluble materials, because excretion rate is excessive and/or because water conservation is extreme, crystals form and may grow and aggregate to form a stone (2).

So, nephrolithiasis is a disease that presents an increased urinary concentration of stone-forming salts and urine volume is a major determinant of the concentration of this lithogenic factors. Fluid intake is the main determinant of urine volume and therefore, as several observational studies (3-5) and a randomized controlled trial (6) have demonstrated, higher fluid intake reduces the risk of stone formation. Also, a prospective trial affirms that increased water intake also prolongs the average interval between recurrences (7).

1.2. PREVALENCE:

Kidney stone disease is a common malady, affecting nearly 1 in 11 individuals in the US at some point in their lives and there is evidence that the number of those who have had a stone is rising (8), with at least 50% of individuals experiencing another stone within 10 years of the first occurrence (9). Historically, kidney stones have occurred more commonly in men than in women, although the gender gap in stone disease is closing (10-12).

The reasons for the observed rise in stone disease among women are not certain, but the impact of obesity, a known risk factor for kidney stones, was found to be greater in women than in men (13). In fact, obesity is an independent risk factor for urinary calculi, particularly in women (14), reason why weight loss is desirable in these patients. Additionally, the beneficial effect of dietary moderation in reducing the risk of recurrent stones was demonstrated by Hoskings and co-workers, who found a reduction in stone recurrence rate among 108 idiopathic calcium oxalate stone formers who were encouraged to maintain a high fluid intake and avoid “dietary excess” (15).

1.3. ECONOMIC IMPACT:

Symptomatic urolithiasis manifests robustly in the practice of the Emergency Department (ED) physician, with a significant economic impact that echoes beyond the ED visit. It has been reported that over 8´8% of the United States population will be affected by this malady, and when treatment costs, sick days from work and third-party payments are considered, costs around $2.1 billion per year to the US economy alone (8, 11, 16, 17). Sadly, no article was found on the economic impact of the renal colic in this country, not even in the Intern resident book from the Spanish Association of Urology (18).

1.4. SYMPTOMATOLOGY:

Renal colic from an obstructing calculus presents classically with sudden-onset, severe and sharp pain localized to the flank, which increases over the following 20-60 minutes, with radiation to the lower abdomen, groin or genitals. It is often accompanied by nausea and vomiting. Urinary symptoms,

most commonly frequency and urgency with low voided volumes, are common in distal ureteral stones (19). Other possible symptoms are pain on micturition, strangury and/or interruption of urine flow (1, 2). However, not all patients presenting with flank pain have urinary calculi, so an important aspect of the initial evaluation is to search for other potential diagnoses (**Table 1**) (20).

Table 1. Differential Diagnosis for Urinary Calculi.

CLINICAL CLUES	SUGGESTED DIAGNOSIS
Anorexia, nausea, vomiting	Obstructing urinary calculi, bowel disease
Dysuria	UTI, urinary calculi, interstitial cystitis
Fever, chills	Viral o bacterial illness
Hematuria (microscopic or gross)	Urinary calculi, urothelial tumor, UTI, BPH, renal mass
Hemodynamic instability	Nonspecific findings of shock (including possible sepsis)
Inability to get comfortable	Urinary calculi, peritonitis
Pain and tenderness • Abdominal pain • Flank pain (sharp, extreme pain with sudden onset) • Flank tenderness • Groin pain (scrotal, labial) • Penile or pelvic pain • Suprapubic tenderness Tachycardia Urinary frequency	 Small renal calculi, nonurologic etiology (GI origin) Urinary calculi, musculoskeletal spasm Urinary calculi, musculoskeletal inflammation, pyelonephritis Ureteral calculi, hernia, testicular mass Ureteral calculi, urethritis, prostatitis UTI, interstitial cystitis, prostatitis, urinary calculi, peritonitis Nonspecific response to pain UTI, ureteral calculi, BPH

UTI = Urinary Tract Infection; BPH = Benign Prostatic Hyperplasia.

1.5. DIAGNOSIS:

A typical work-up includes a thorough history and physical examination, serum chemistry and complete blood count, urinalysis, and an imaging study. Typical laboratory findings are presented in **Table 2** (20).

Table 2. Clinical Clues to the Diagnosis of Urinary Calculi.

EVALUATION	POSSIBLE FINDINGS
Laboratory evaluations	
Complete blood cell count	Leukocytosis with struvite calculi
Serum chemistry	Elevation in creatinine levels with obstructing calculi; hypokalemia and hyperchloremia with Renal Tubular Acidosis; elevated serum calcium levels with parathyroid disease
Serum parathyroid hormone levels	Elevated in hyperparathyroidism
Urinalysis	Microscopic or gross hematuria; acidic urine; alkaline urine (with struvite calculi); pyuria; crystals from involved calculi
24-hour analysis	Elevated urinary calcium, oxalate, and sodium levels; decreased urinary volume and citrate levels

Most patients have remediable metabolic disorders that cause stones, so the composition of kidney stones should be determined when possible, because treatment depends on stone type (**Table 3**) (1). Stone composition of uric acid, cystine or struvite implicates specific metabolic or genetic abnormalities and knowledge of stone composition may also help direct preventive measures (21, 22). Regarding the metabolic testing, there are conflicting opinions in the literature about the adequacy of a single 24-hour urine in reliably identifying urinary abnormalities (23-27). In the absence of clear consensus, either one or two 24-hour urines may be obtained, although two collections are preferred.

Table 3. Major Causes of Renal Stones.

STONE TYPE	PERCENT of all stones[a]	PERCENT occurrence of specific causes[a]
CALCIUM STONES: 75-85%		
Idiopathic calciuria		50-55%
Hypocitraturia		20-40%
Dietary hyperoxaluria		10-30%
Hyperuricosuria		20%
Idiopathic stone disease		20%

URIC ACID STONES: 5-15% Metabolic syndrome _____ Gout _____ Idiopathic _____	 30% 30% 30%
STRUVITE STONES: 5%	
CYSTINE STONES: 1%	

[a] Values are percentages of patients who form a particular type of stone and who display each specific cause of stones.

Regarding imaging studies, non-contrast computed tomography (CT) has emerged as the most sensitive and specific modality for detecting ureteral calculi. Consequently, CT is frequently used in the initial diagnosis of ureteral calculous disease (28) and in the follow-up of known ureteral calculi before and after treatment. Additionally, conventional radiography and ultrasound are endorsed for monitoring the passage of most radiopaque stones (29). Ultrasound is has a relatively low sensitivity, although it is often used as the initial imaging test in pregnant patients with flank pain (30). Typical radiographic findings are presented in **Table 4** (20).

Table 4. Clinical Clues to the Diagnosis of Urinary Calculi.

EVALUATION	POSSIBLE FINDINGS
Radiographic evaluations	
Abdominal, kidney and upper bladder radiography	Urinary calculi larger than 2 mm may be visible
CT (stone protocol)	Nearly all calculi are visible on CT. Evaluates renal parenchyma, hydronephrotic changes and surrounding organs
Intravenous pyelography	Calculi visible on scout film. Delay in contrast excretion if obstruction is present. Calculi may appear as filling defect
MRI	Conventional MRI is not useful for imaging calculi
Ultrasonorography	Calculi appear as hyperechoic lesions that cast acoustic shadows. Not reliable for ureteral calculi. May demonstrate dilation of collecting system

CT = computed tomography; MRI = magnetic resonance imaging.

1.6. TREATMENT:

All patients should be counseled to avoid dehydration and drink copious amounts of water (1). An important study confirmed that increasing urine volume to 2.5 L per day resulted in a 50% reduction of stone recurrence compared with the control group (6).

Firstly, stones not causing obstruction may be managed conservatively. We should provide immediate pain relief, offering a non-steroidal anti-inflammatory drug (NSAID) as the first drug of choice (30). NSAIDs decrease the production of arachidonic acid metabolites, mediators of the pain response released by the stretch of the renal capsule due to downstream obstruction. In addition, they cause contraction of the afferent arterioles to the glomerulus, thereby decreasing hydrostatic pressure by reducing glomerular filtration rate. They are safer than opioids, which could cause depression of level of consciousness and respiratory drive. However, caution should be exercised in the elderly and those with renal impairment (19).

Literature suggests that a combination approach with NSAIDs and opioids may be the most effective method to manage renal colic in the ED (31). This combination has been studied in numerous comparisons. A systematic review recommends parenteral NSAIDs be used as first-line therapy for patients with renal colic, with the use of narcotics as adjuvant or breakthrough analgesia (32). Paracetamol has also proved to be an effective analgesic for acute colic. A recent trial showed no significant difference between degree of pain control and time to relief between iv paracetamol and iv morphine, with fewer adverse effects in the paracetamol group (33).

Moreover, Medical Expulsive Therapy (MET) may be used if needed, as it increases luminal diameter and inhibits smooth muscle tone in the ureter and ureterovesical junction. These effects have been accomplished with the use of steroids and NSAIDs to limit inflammation-induced narrowing of the ureteral caliber. This combination has commonly been used in concert with agents intended to relax ureteral smooth muscle to decrease painful spasm and to potentially dilate the upper urinary tract to decrease pain (19).

The presence of adrenergic receptors in the human ureter (with increasing density in the distal ureter), the preponderance of the α-1 subtype and the ability of α-blocking medication to decrease ureteral contractility are well established (34-36). Calcium channel blockers (CCB) have also shown relaxing effects on ureteral smooth muscle (37).

Multiple studies suggest that these agents augment the stone expulsion rate when compared with standard therapy (38-49), although taking a closer look at the reliability of this studies, the efficacy of tamsulosin and MET in improving the spontaneous passage of kidney stones is unclear. However, given that this therapy is generally well tolerated and may improve the rate of expulsion of kidney stones, a trial of tamsulosin or nifedipine may be considered at discharge. Based on the literature, α1-adrenergic blockers are preferred to CCB, due to shorter time to stone passage and fewer adverse effects (31).

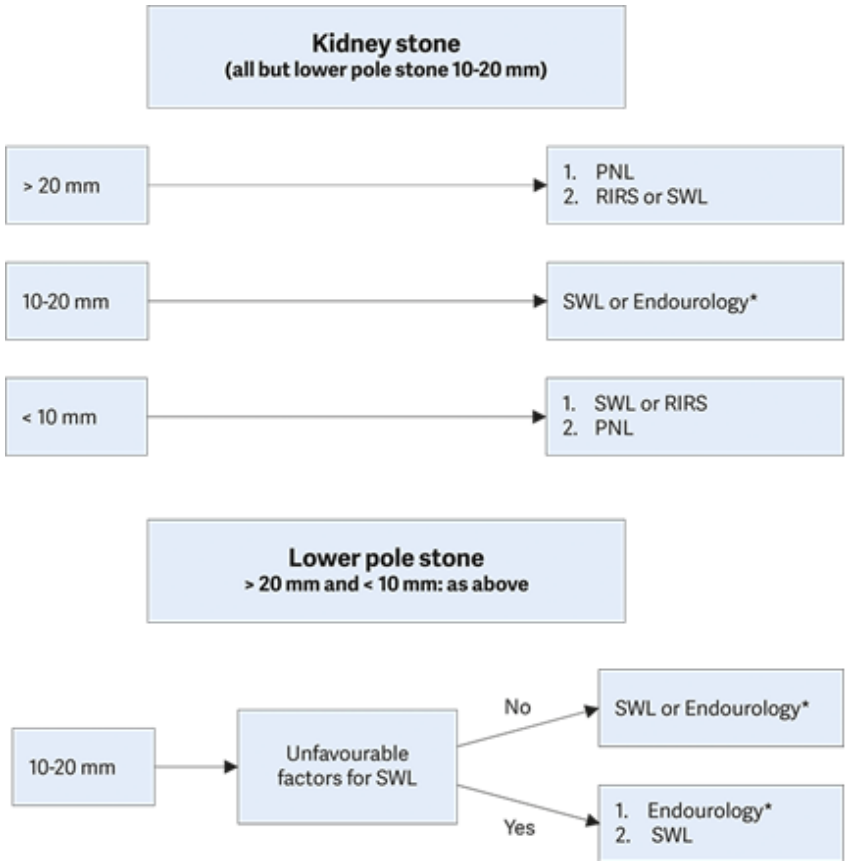
Furthermore, if the stone passes into the ureter and does cause obstruction, it becomes a complicated renal colic which can reduce both glomerular filtration rate and renal blood flow. The indications for urgent intervention in urinary tract obstruction are: presence of infection or urosepsis, intractable pain and/or vomiting, impending acute renal failure, obstruction with a solitary or transplanted kidney and bilateral obstructing stones (50).

At the Emergency Department of Cruces Universitary Hospital, urine derivation is practiced when urgent intervention is required, mostly with a single J (single end single loop) or a double J (both end single loop) catheter. If insufficient, a nephrostomy is carried out, with or without the infusion of an alkalizing treatment such as sodium bicarbonate or alkaline citrate. A randomized controlled trial found that ureteral catheters, ureteral stents, and percutaneous nephrostomy tubes are equally effective for decompressing the urinary tract (51). Lastly, flexible or rigid ureterorenoscopy plus intracorporeal lithotripsy can be used as first or second line treatment and once or more.

Secondly, the interventional approach of nephrolithiasis usually takes place as second-line treatment. Therefore, I´ll simply mention it, as the bottom-line of this project is the acute treatment for the renal colic. Truly, advances in

urologic technology have rendered open surgery for stones a rare event, leaving three alternatives: extracorporeal shockwave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) and ureterorenoscopy (URS) (**Figures 1 and 2**). In general terms, the main contraindications for SWL and PNL are pregnancy, untreated urinary tract infections, bleeding diatheses, anticoagulant therapy, severe obesity or skeletal malformations (only SWL)... On the other hand, URS has no specific contraindications, apart from those related to the general anesthesia and the untreated urinary tract infections (30).

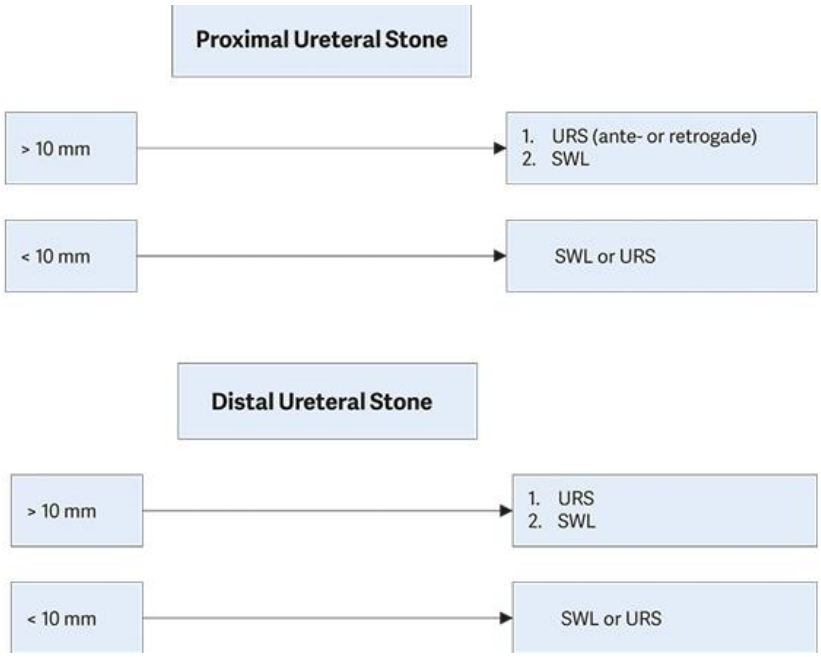
Figure 1. Treatment algorithm for renal calculi (30).



*The term "Endourology" encompasses all PNL and URS interventions.

PNL=percutaneous nephrolithotomy; RIRS=retrograde renal surgery; SWL=shockwave lithotripsy; URS=ureterorenoscopy.

Figure 2. Treatment algorithm for ureteral calculi (GR: A*) (30).



SWL=shockwave lithotripsy; URS=ureterorenoscopy.

As you read through the introduction, you can notice the wide range of possibilities available for the treatment of the kidney stones. In fact, while working on this research, I found myself diving in a vast ocean of information about how renal colic´s acute pain and kidney stones in general should be treated. As a result, I decided to search for information available and compared the effectiveness of two of the main approaches of this illness: the European protocols and the protocols followed in the USA. Finally, I´ll be focusing particularly on analyzing the protocol that we follow at Cruces University Hospital, hoping to reach some conclusions regarding its high, intermediate, or low effectiveness in the acute kidney stone treatment.

2. HYPOTHESIS / OBJECTIVES

To frame and give shape to the end-of-career project is essential to define its objectives. The following are the hypothesis that´ll be the bottom line of this project:

2.1 Searching for significant similarities and/or differences in the protocols stated by Europe and United States of America on the treatment of urolithiasis. For this, I´ll be comparing the official European Urology Association (EAU) guidelines on urolithiasis and the official American Urological Association (AUA) guidelines on medical and surgical management of kidney stones.

2.2 Searching for valid, significant and current comparative studies between the effectiveness of either the diagnosis and the medical or surgical treatment for nephrolithiasis in Europe and USA. For this, I´ll be using globally recognized databases on health sciences.

2.3 Analyzing the protocol that we follow at Cruces University Hospital for the diagnosis and treatment of acute kidney stone in the emergency room, and looking for similarities or differences with the European and the American guidelines on urolithiasis or other reliable sources of information.

2.4 Reaching some conclusions regarding the most effective treatment for the renal colic in the emergency room, built upon high level of evidence data if possible.

3. MATERIAL AND METHODS

This project is a Literature Review for which the main source of information was Cruces University Hospital´s online library service for Health sciences. This library allows access to a wide range of worldwide recognized databases such as Ovid, Clinical Access, Cochrane, Fisterra, UpToDate, Clinical Key, Micromedex, etc.

Precisely, this investigation has been constructed through a search in Ovid database, which contains publications on JBI/Joanna Briggs Institute, EMBASE, MEDLINE, DIF/Drug Information Full text, IPA/International Pharmaceutical Abstracts, PsycINFO and LWW books and journals. Also, with articles from PubMed and information obtained from Harrison´s principles of internal medicine and Oxford handbook of clinical medicine. The online information was searched using combinations of the following key words:

3.1 ‘acute’ +‘renal’ + ‘colic’ + ‘treatment’
3.2 ‘renal’ + ‘colic’ + ‘emergency’+ ‘protocols’
3.3 ‘urolithiasis’ + ‘emergency’ + ‘department’
3.4 ‘nephrolithiasis’ + ‘emergency’ + ‘department’
3.5 ‘effectiveness’ + ‘protocols’ + ‘calculus’
3.6 ‘management’ + ‘nephrolithiasis’ + ‘emergency’ + ‘department’
3.7 ‘renal’ + ‘colic’ + ‘medical’+ ‘expulsive’+ ‘therapy’
3.8 ‘kidney’ + ‘stones’ + ‘medical’ + ‘expulsive’ + ‘therapy’
3.9 ‘urgent’ + ‘decompression’ + ‘ureteral’ +‘calculi’
3.10 ‘water’ + ‘urinary’ + ‘volume’ + ‘nephrolithiasis’
3.11 ‘urgent’ + ‘decompression’ + ‘ureteral’ + ‘calculi’

The studies included were published from 1972 to 2017 and recent articles were given highest priority because they represent the current state-of-the-art treatment. Meanwhile, older studies were included selectively if historically relevant or if they addressed issues more adequately than the more recent literature. The paper search was limited to the English language, although a reference from a Spanish source can also be found. The European Association of Urology (EAU) and American Urological Association (AUA) guidelines were used in order to assemble appropriate evidence-based reference literature.

The topics of these guidelines were selected based on the level of evidence A or B, as described by the Oxford Centre for Evidence-Based Medicine Levels. In this source, when sufficient evidence exists, the body of evidence for a particular clinical action is assigned a strength rating of A (high), B (moderate) or C (low). Additionally, the AUA nomenclature system links strong, moderate or conditional recommendation to the A, B or C levels of evidence. Also, in the absence of sufficient evidence they provide additional information as Clinical Principles and Expert Opinions.

4. RESULTS

The main results of this bibliographic review are obtained from two of the chief sources of information used: the guidelines on urolithiasis from the EAU and the AUA. As we mentioned before, we´ll extract only the principles that are supported by A or B levels of evidence. These principles have been arranged in two columns, one for each source, so that we can easily compare the principles that describe same topic. Some data with lower level of evidence has also been included (grade C, Clinical Principles -CP- and Expert Opinions -EO), only because its comparison with the equivalent topic from the other source is considered relevant. For the reader´s convenience, this low evidence data is marked with an orange background.

4.1 DIAGNOSIS: Imaging.

European Association of Urology (EAU) (30)	GR	American Urological Association (AUA) (52)	GR
Following initial ultrasound assessment, use non-contrast-enhanced CT to confirm stone diagnosis in patients with acute flank pain, as it is superior to intravenous urography.	A	Non-contrast CT (NCCT) is the preferred initial imaging study for the adult patient.. The diagnostic accuracy of non-contrast CT in identifying ureteral calculi is the following: sensitivity 98% and specificity 97%.	A
In children, use ultrasound as first-line imaging modality when a stone is suspected. Perform a KUB X-ray (or low-dose non-contrast-enhanced CT) as an alternative.	B	Renal ultrasonorography is the preferred initial imaging study for pediatric patients (<14).	C
Use ultrasound as the preferred method of imaging in pregnant women.	A	Renal ultrasonorography is the preferred initial imaging study for pregnant patients.	C

4.2 DIAGNOSIS: Additional testing.

European Association of Urology (EAU) (30)	GR	American Urological Association (AUA) (53)	GR
Perform stone analysis in first-time formers using a validated procedure.	A	When a stone is available, clinicians should obtain a stone analysis at least once.	CP
Repeat stone analysis in patients with recurrent stones despite drug therapy, early recurrence after stone clearance or late recurrence after a long stone-free period.	B	Clinicians should repeat a stone analysis, when available, especially in patients not responding to treatment.	EO
Only high-risk stone formers (all children, recurrent stone formers, transplanted kidneys...) require specific metabolic evaluation after stone removal.	A	Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers.	B

4.3 TREATMENT: Conservative management.

European Association of Urology (EAU) (30)	GR	American Urological Association (AUA) (53)	GR
Provide immediate pain relief in acute stone episodes. Whenever possible, offer a NSAID as the first drug of choice. E.g. metamizol.	A		
Offer hydromorphine, pentazocine or tramadol as a second choice.	C		
In patients with newly diagnosed from small ureteral stones, if active stone removal is not indicated, observe patient periodically.	A	Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy.	A
Follow-up periodically in cases where renal stones are not treated (initially after six months and then yearly, evaluating symptoms and stone status [either by ultrasound, KUB radiography or CT]).	A	Clinicians should periodically obtain follow-up imaging studies to asses for stone growth or new stone formation based on the stone activity (plain abdominal imaging, renal ultrasonography or low dose computed tomography [CT])	EO
Offer α-blockers as MET as one of the treatment options, in particular for (distal) ureteral stones > 5 mm. Counsel patients regarding the controversies in the literature, attendant risks of MET, including associated side effects. Inform that α-blockers as MET are administered off-label⌖.	A	Patients with uncomplicated ureteral stones <10 mm should be offered observation, and those with distal stones of similar size should be offered MET with α-blockers. In pediatric patients with uncomplicated ureteral stones ≤10 mm, offer observation with or without MET using α-blockers.	B
Recommend a high fluid intake (2.5-3 L/day) in patients with a small urine volume.	A	Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 liters daily.	B
Recommend a high fluid intake (2.5-3 L/day) in patients with no abnormality identified in urine composition.	B		

4.4 TREATMENT: Interventional/endoscopic management.

European Association of Urology (EAU) (30)	GR	American Urological Association (AUA) (54)	GR
Obtain a urine culture or perform urinary microscopy before any treatment is planned. Exclude or treat urinary tract infection prior to endourological stone removal.	A	Clinicians are required to obtain a urinalysis prior to intervention. In patients with clinical or laboratory signs of infection, urine culture should be obtained.	B
Perform retrograde (flexible) URS if stone removal is essential and antithrombotic therapy cannot be discontinued, since it is associated with less morbidity.	A	Clinicians should use URS as first-line therapy in most patients who require stone intervention in the setting of uncorrected bleeding diatheses or who require continuous anticoagulation / antiplatelet therapy.	C

Offer perioperative antibiotic prophylaxis to all patients undergoing endourological treatment.	A	Antimicrobial prophylaxis should be administered prior to stone intervention and is based primarily on prior urine culture results, the local antibiogram, and in consultation with the current BPS on Antibiotic Prophylaxis.	CP
Treatment algorithm for RENAL CALCULI (if indicated for active stone removal): I. Kidney stone: - >20mm: 1º PNL and 2º URS/SWL. - 10-20mm: SWL/URS/PNL - <10mm: 1º SWL/URS and 2º PNL. II. Lower pole stone: - 10-20mm: 1º SWL (if possible) and 2º URS/PNL. In complex stone cases, use open or laparoscopic approaches as an alternative	B	In patients who fail or are unlikely to have successful results with SWL and/or URS, clinicians may offer PNL, laparoscopic, open, or robotic assisted stone removal.	C
Treatment algorithm for URETERAL CALCULI (if indicated for active stone removal): III. Proximal ureteral stone: - >10mm: 1º URS and 2º SWL. - <10mm: SWL or URS. IV. Distal ureteral stone: - >10mm: 1º URS and 2º SWL. - <10mm: SWL or URS.	A	Clinicians should inform patients that SWL is the procedure with the least morbidity and lowest complication rate, but URS has a greater stone-free rate in a single procedure. In patients with mid or distal ureteral stones who require intervention (who were not candidates for or who failed MET), recommend URS as first-line therapy. For patients who decline URS, clinicians should offer SWL.	B
After SWL and URS, and in the presence of residual fragments, offer MET using an alpha-blocker to improve fragment clearance.	A	Clinicians may prescribe α-blockers to facilitate stone fragment passage after SWL and add antimuscarinic therapy for stent discomfort.	B
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except those that have clinical indications for intervention).	A	In pregnant patients with ureteral stones and well controlled symptoms, clinicians should offer observation as first-line therapy.	B

Moving on to the results of other influential articles included in this project, the Review Article named "Renal colic: current protocols for emergency presentations" contains quite the same information found in the EAU and the AUA guidelines regarding diagnosis of urolithiasis. However, in terms of its medical treatment in the Emergency Department (ED) it sheds some light on the guidelines that should be followed. This article mentions several other sources of information, some of which were considered relevant. We found the original articles through the bibliography and summarized the results in the following table (19).

SOURCES	RESULTS
"Systematic review of the relative efficacy of nonsteroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic" (32).	- **NSAIDs achieve slightly greater reductions in pain scores than opioids in patients suffering from renal colic.** - **These patients are less likely to need rescue analgesia if treated with NSAIDs.** - **Opioids are associated with a higher rate of vomiting and other adverse effects.**
"Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomized double-blind controlled trial" (33).	- **IV paracetamol is an effective analgesic for acute renal colic.** - **There was no significant difference between the degree of pain control and time to relief between IV paracetamol and IV morphine.** - **There were fewer adverse effects in the paracetamol group.**
"Renal colic: current protocols for emergency presentations" (19).	- **Active warming of the lower back to 42°C and acupuncture have also shown benefit for pain reduction.** - **Significant improvement in appropriate analgesia usage by simply providing the patient with written (instead of just verbal) instructions before discharge (from 40% to 71% of patients), resulting in increased patient satisfaction.**
Meta-analysis by European Association of Urology (EAU) and American Urology Association (AUA) to form the joint guidelines on urolithiasis in 2007 (55, 56).	- **Nifedipine was associated with a nonstatistically significant 9% increase in stone passage rates, whereas α-blockers were associated with a significant 29% increase in stone passage, up to a size of 10mm.**
"Medical expulsive therapy in adults with ureteral colic: a multicentre, randomized, placebo-controlled trial". The SUSPEND trial in 2015 (57).	- **Comparing nifedipine, tamsulosin and placebo in patients with a CT confirmed ureteral stone, no difference was observed in terms of stone expulsion rates or reduction in analgesia requirements irrespective of stone site or size.**

Next, we will be analyzing the protocol followed at Cruces University Hospital for the diagnosis and treatment of acute kidney stone in the emergency room. This protocol was recently carried out by the Radiology Department in order to standardize the use of imaging studies for patients in the Emergency Department (ED). If imaging study becomes mandatory, then non-contrast-enhanced ADB-PV CT scan is the appropriate study to be carried out. This protocol contains the definition of an uncomplicated renal colic as well as the alarm signs that indicate that´s become complicated (high fever ≥38'5ºC or septic shock/systemic infection signs). The rest is divided in three sections (**Annex 1**):

I. Modulating factors:

I.I. There´s no modulating factors.

I.II. Solitary kidney or transplanted kidney.

I.III. Previous renal impairment or acute renal failure.

I.IV. Clinical suspicion of urinary tract obstruction (oliguria/anuria).

I.V. Intractable pain after 1h.

I.VI. Abrupt pain recurrence after effective initial analgesia (readmission in <48h).

I.VII. Persistent nausea and vomiting.

I.VIII. Need for differential diagnosis: men >60 years old with left flank pain (acute aortic syndrome must be discarded).

Each of these modulating factors can be clicked if present. The instructions to follow can be found next to this list, which are the following: in case there´s no modulating factors: do not request X-Rays or do approach Radiologist. In case of ≥1 modulating factor: request non-contrast-enhanced ABD-PV CT. In case previous radiopaque calculi history: request ABD X-Rays +/- Ultrasound. Lastly, in children 14 to 18 years old or pregnant patients: request ABD Ultrasound (**Annex 1**).

II. Recommended analgesia for uncomplicated renal colic:

II.I. Begin treatment with IV dexketoprofen (50mg) and IV paracetamol (1g).

II.II. Provide IV morphine (3mg) in case there´s no improvement.

II.III. If nausea or vomiting, combine with primperam or yatrox.

II.IV. Consider individual changes (if allergies, possible interactions with active medical treatments).

III. Recommendation after patient discharge:

III.I. Regular analgesia at the treating physician´s discretion: NSAIDs + 1st and 2nd step analgesics + weak opioid as rescue medication.

III.II. Without modulating factors: follow up by family physician, who will decide further outpatient clinic checkups and supplementary tests.

III.III. With modulating factors, refer patient to the urologist.

5. DISCUSSION

5.1 GENERAL ASPECTS

While comparing the EAU and the AUA guidelines on urolithiasis, there´s one disparity that quickly catches the reader´s eye and that is the big difference between the low evidence data among the principles included in the document. As you can see, there´s eight low evidence based principles in the AUA, versus only one in the EAU. **In other words, the EAU generally holds best evidence supported principles** (16 A-s, 6 B-s and only 1 C), **while the AUA includes a big amount of low evidence based data** (3 A-s, 8 B-s, 4 C-s, 2 Clinical Principles and 2 Expert Opinions) (30, 52-54).

5.2 DIAGNOSIS: IMAGING STUDIES

As for the diagnosis, the **non-contrast-enhanced CT (NCCT) is the preferred initial imaging study for the adult patient with acute flank pain**. This is one of the most important principles included in the guidelines, which quickly calls our attention also because it happens to be one of the only two principles that share evidence level A in both EAU and AUA guidelines. On top of that, the AUA supports by an A level of evidence the diagnostic accuracy of this imaging study, which are 98% sensitivity and 97% specificity.

On the other hand, the **ultrasound** should be used as **the preferred first-line imaging modality in children and pregnant women** suffering from a renal colic. However, this is supported by strong evidence in the EAU (B and A respectively) while is supported by weak evidence in the AUA (C for both). The reason why these analogous principles present such uneven levels of evidence remains unknown.

5.3 ADDITIONAL TESTING AND MEDICAL TREATMENT

Either with or without strong recommendation, the guidelines affirm that a stone analysis should be carried out in first-time stone formers, repeating it depending on particular circumstances. This should always be done, as the final composition of the stone will be shedding light on the steps to follow for its management and definitive treatment.

Additionally, the guidelines state that the metabolic evaluation is particularly required in high-risk stone formers, supported by strong evidence. Taking a closer look at this, one can wonder what being a high-risk stone former means. **In fact, we believe that the stone analysis and the following metabolic testing are actually the resources that will give physicians enough information to categorize a patient as a high or low risk stone-former, reason why they should both be mandatory in all first-time stone formers.**

For instance, if we found the most common type of stones, Calcium stones, we will be doing further metabolic testing to search for idiopathic calciuria, hypocitraturia… among others. On the other hand, if we found uric acid stones, then we would be studying the patient´s cardiovascular risk factors, presence of gout… (see **Table 3**).

Regarding the use of MET, the mentioned **SUSPEND trial was the most robust, well-powered study to date and it dismissed the role of tamsulosin and nifedipine as part of this treatment in 2015 (57).** Such was the relevance of this study, that the following year, "Medical Expulsive Therapy for Ureterolithiasis: The EAU Recommendations in 2016" was published. In it, the EAU explained how lots of publications over the years had supported the use of α-blockers as MET, although several recently published high quality, large, placebo-controlled randomized trials raised serious doubts about the effectiveness of α-blockers (58).

Moreover, in the latest update of **the EAU guidelines on urolithiasis (2017)**, strong evidence still supports the use of MET in distal ureteral stones and also to facilitate passage of residual fragments after SWL and URS. However, to this first recommendation, the EAU guidelines add a couple of principles that seem cautious and ambiguous at the same time. They state that **patients should be counseled regarding controversies in the literature, associated side effects (hypotension being the most frequent)** as well as informing them that α-blockers as MET are administered off-label. This couple of principles **reflect, again, the EAU´s rectification** after the SUSPEND trial came to light.

Furthermore, attached to these ambiguous principles, two precise footnotes can be found: one, that it is not known if tamsulosin harms the human fetus or if it is found in breast milk and two, that **MET using α-blockers in children and during pregnancy cannot be recommended due to the limited data in this specific population**. On the other hand, **the AUA states that in pediatric patients** with uncomplicated ureteral stones ≤10 mm, clinicians should **offer observation with or without MET using α-blockers**. This is a big disparity between the two sources.

So not only in adult patients but there´s also great controversy about the use of MET in children, which added to the controversy raised up by the SUSPEND trial about the inefficacy of MET (57), generates **doubt about the truthfulness of the original studies that supported the launching of this medication into market.** In fact, all of this leads us to think that substantial commercial interests from influential pharmaceutical companies could probably be underneath the overcome MET fever.

Moving on, the **perioperative antibiotic prophylaxis in all patients undergoing endourological treatment is supported with strong evidence by the EAU** (A level of evidence), while is supported with weak evidence by the AUA (Clinical Principle). The reason why these analogous principles present such uneven level of evidence remains unknown. However, this prophylaxis **should be considered a must, as it is generally known that the stones have quite a high probability of infection** and administrating the antibiotics by protocol could save time and money to the system, as well as potential complications to the patient.

5.4 CRUCES UNIVERSITARY HOSPITAL´S PROTOCOL FOR THE TREATMENT OF THE RENAL COLIC IN THE EMERGENCY DEPARTMENT

Overall, this protocol follows quite strictly the established European and American guidelines on the treatment of urolithiasis. Firstly, it declares the **non-contrast-enhanced ABD-PV CT scan as the standardized imaging study**. Secondly, this protocol also declares the **ABD ultrasound as the**

preferred imaging study for children and pregnant women, which meets all the criteria from the mentioned sources.

Thirdly, the modulating factors included in the protocol are the so called standard indications for urgent intervention, which we have seen earlier in the "Management of kidney stones" article: presence of infection or urosepsis, intractable pain and/or vomiting, impending acute renal failure, obstruction with a solitary or transplanted kidney and bilateral obstructing stones (50). This protocol goes even slightly further, as it includes another indication: the need for a differential diagnosis in case of men over 60 years old with left flank pain, as we must discard an acute aortic syndrome.

Regarding the medical treatment of the renal colic, the **analgesics included in the protocol are IV NSAID (dexketoprofen) as the first drug of choice and iv paracetamol, same as stated by the EAU with an A level of evidence.** As a second choice analgesic, the protocol includes IV morphine, even though the EAU supports this with a C level of evidence. Surprisingly, this protocol **does not mention the use of α-blockers as MET**, which is recommended by the EAU in particular for distal ureteral stones >5 mm with an A level of evidence. Again, this could be due to the existing controversy about the efficacy of MET, reflected in the SUSPEND trial as we mentioned earlier.

6. CONCLUSIONS

6.1 GENERAL ASPECTS

While completing the introduction of this project, the first conclusion we reached was that there´s a **national lack of investigation on this topic. Regardless of how common the renal colic is among the population, no article could be found on the prevalence or the economic impact of this disease in the country.** Economical data from the US was used to complete this project, as the country enjoys widely supported researching resources.

However, we should again highlight the fact that the **European guidelines on urolithiasis generally hold best evidence supported principles, while the AUA includes a big amount of low evidence based data**, even though the reason for such uneven levels of evidence remains unknown.

6.2 DIAGNOSIS: IMAGING STUDIES

As we mentioned before, the **non-contrast-enhanced CT scan has proved to be the most worthwhile imaging study for the diagnosis of urolithiasis**, although it must be used rationally. Also, the **ultrasound** should be used as **the preferred first-line imaging study in children and pregnant women** suffering from a renal colic.

6.3 ADDITIONAL TESTING AND MEDICAL TREATMENT

T**he stone analysis and the metabolic testing** of the patients with urolithiasis is a determining procedure for a more precise treatment in stone-formers. **We realized that there is no standardized protocol for this in Cruces University Hospital**, resulting in a random chance of performing the tests depending on the attending physician. **We encourage the hospital to develop one,** as this will provide a rising and spreading awareness to perform both the stone analysis and metabolic testing, especially between the most inexperienced physicians. Eventually, this would lead to a more precise treatment/intervention/prevention program, which would also lead to lower chances of recurrent renal colic, which would at the same time turn into lower spending rates for the system.

Regarding the medical treatment of the renal colic, it´s safe to affirm that we have found the answer to our most primitive question, the question that originated this project. **Yes, there is an ideal treatment for the acute renal colic,** built in fact, upon high level of evidence data. This is based on **IV NSAIDs plus IV paracetamol, to which IV opioids such as morphine can be added up in case the pain is still uncontrolled**. On the other hand, we discovered that highly accurate and reliable sources have proved **MET with α-blockers to be ineffective in the treatment of urolithiasis**.

As we have already mentioned, there´s strong evidence supporting **perioperative antimicrobial prophylaxis** to all patients undergoing endourological treatment. We also found that there´s **no standardized protocol for this in Cruces University Hospital, so we encourage them to develop one** in order to diminish the chances of mistake.

6.4 CRUCES UNIVERSITARY HOSPITAL´S PROTOCOL FOR THE TREATMENT OF THE RENAL COLIC IN THE EMERGENCY DEPARTMENT

With all the data found and all the comparisons made, we stand in absolute favor of this protocol, as it is not only based on theoretical high level of evidence data from reliable sources, but has also proved to be profitable in the long run for the applied patient´s assistance, despite the initial distrust and skepticism that caused. In fact, **including the non-contrast-enhanced CT scan in this protocol has provided higher accuracy on the diagnosis of urolithiasis and on the consequent medical and/or interventionist/surgical treatment, as well as helping with the early detection of accidental discoveries such as cancer or metastasis in any abdominal organ.**

6.5 INTERVENTIONAL TREATMENT

Finally, we found that SWL is the procedure with the least morbidity and lowest complication rate, while URS has a greater stone-free rate in a single procedure. Meanwhile, there´s also strong evidence supporting that **PNL** should be the initial interventional treatment of choice **for large kidney stones (>20mm), while smaller kidney stones or lower pole stones should ideally**

be treated with SWL. Meanwhile, there´s also strong evidence supporting **larger ureteral stones (>10mm**, no matter if higher or lower location) should be **initially approached with URS, while smaller stones (<10mm,** no matter if higher or lower location) **should be first treated with SWL**.

7. RECOMMENDATIONS TO THE HEALTH SERVICE

7.1 Research on the outcomes of any intervention should be more encouraged in all hospital services, as a way to guarantee that the right measures are being put into practice for the system´s improvement. In our case, **we recommend researching on the effectiveness of Medical Expulsive Therapy (MET) treatment for urolithiasis in our community**.

7.2 Create **protocols for the metabolic testing as part of the renal colic´s general study, as well as for the prophylactic administration of antimicrobial therapy** in patients with urolithiasis that require intervention. Ideally, after creating and applying the protocols, research should be encouraged in order to evaluate the outcomes.

7.3 Cruces Universitary Hospital´s protocol for the treatment of the renal colic in the emergency department has proved to be effective, so its integration in other health institutes should be considered. For this, Emergency Departments should be supplied with CT scans in order to facilitate their use as the everyday diagnostic study.

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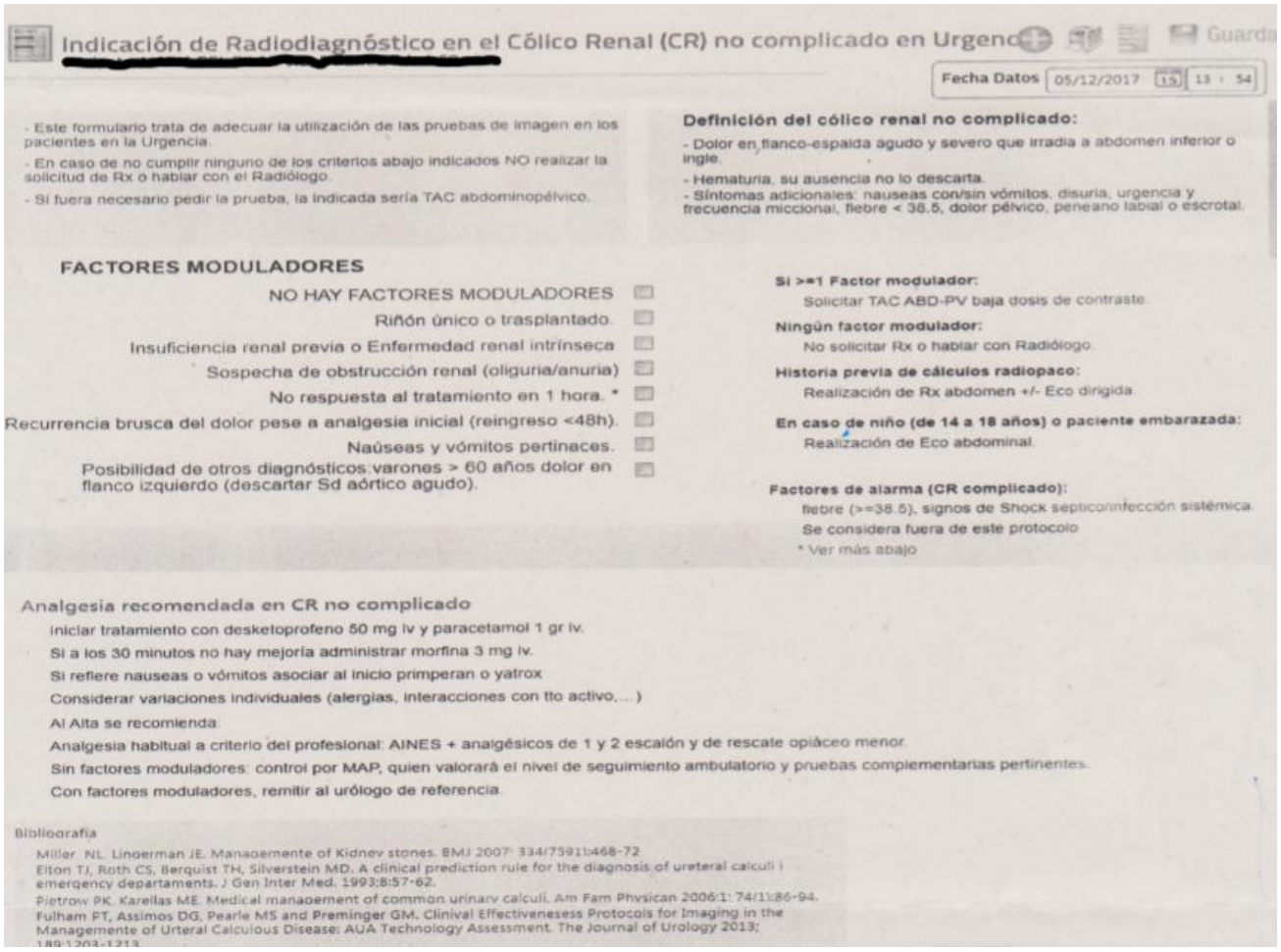
ANNEXES

ANNEX 1



Indicación de Radiodiagnóstico en el Cólico Renal (CR) no complicado en Urgenc

Guarda

Fecha Datos 05/12/2017 15 13 : 54

- Este formulario trata de adecuar la utilización de las pruebas de imagen en los pacientes en la Urgencia.
- En caso de no cumplir ninguno de los criterios abajo indicados NO realizar la solicitud de Rx o hablar con el Radiólogo.
- Si fuera necesario pedir la prueba, la indicada sería TAC abdominopélvico.

Definición del cólico renal no complicado:

- Dolor en flanco-espalda agudo y severo que irradia a abdomen inferior o ingle.
- Hematuria, su ausencia no lo descarta.
- Síntomas adicionales: nauseas con/sin vómitos, disuria, urgencia y frecuencia miccional, fiebre < 38.5, dolor pélvico, peneano labial o escrotal.

FACTORES MODULADORES

- NO HAY FACTORES MODULADORES
- Riñón único o trasplantado.
- Insuficiencia renal previa o Enfermedad renal intrínseca
- Sospecha de obstrucción renal (oliguria/anuria)
- No respuesta al tratamiento en 1 hora. *
- Recurrencia brusca del dolor pese a analgesia inicial (reingreso <48h).
- Naúseas y vómitos pertinaces.
- Posibilidad de otros diagnósticos:varones > 60 años dolor en flanco izquierdo (descartar Sd aórtico agudo).

Si >=1 Factor modulador:
Solicitar TAC ABD-PV baja dosis de contraste.

Ningún factor modulador:
No solicitar Rx o hablar con Radiólogo.

Historia previa de cálculos radiopaco:
Realización de Rx abdomen +/- Eco dirigida.

En caso de niño (de 14 a 18 años) o paciente embarazada:
Realización de Eco abdominal.

Factores de alarma (CR complicado):
fiebre (>=38.5), signos de Shock septico/infección sistémica.
Se considera fuera de este protocolo
* Ver más abajo

Analgesia recomendada en CR no complicado

Iniciar tratamiento con desketoprofeno 50 mg iv y paracetamol 1 gr iv.
Si a los 30 minutos no hay mejoría administrar morfina 3 mg iv.
Si refiere nauseas o vómitos asociar al inicio primperan o yatrox
Considerar variaciones individuales (alergias, interacciones con tto activo,...)
Al Alta se recomienda:
Analgesia habitual a criterio del profesional: AINES + analgésicos de 1 y 2 escalón y de rescate opiáceo menor.
Sin factores moduladores: control por MAP, quien valorará el nivel de seguimiento ambulatorio y pruebas complementarias pertinentes.
Con factores moduladores, remitir al urólogo de referencia.

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