



**REVIEW ARTICLE**

**Prostatic Hyperplasia and Existing Treatment**

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**ABSTRACT**

Prostatic hyperplasia is noncancerous growth of cells within the prostate gland. It is a progressive condition associated with prostate enlargement (vol. more than 30 ml) as it progresses it is associated with decreased urinary flow, worsening urinary symptoms and long term complications such as bleeding, acute urinary retention (AUR), infection and stones. Prostate is regulated by especially dihydrotestosterone (DHT) which binds to androgen receptor to form complex that causes intracellular events, production of growth and signaling factors that regulate cell division and proliferation of the prostate. 5- $\alpha$  reductase inhibitors like finasteride, dutasteride decrease the production of dihydrotestosterone within the prostate which decreases the prostate volume, increases peak urinary flow rate, decreases risk of acute urinary retention.  $\alpha_1$  adrenergic receptor antagonist like terazosin, doxazosin and tamsulosin decreases lower urinary tract symptoms and increase urinary flow rate but do not reduce the long term risk of urinary retention or need for surgical intervention. There is new interventional therapy like Transurethral Needle Ablation (TUNA), Microwave Thermotherapy, Ethanol Injection therapy but recent advance technique like photoselective vaporization of prostate for treatment of prostatic hyperplasia disease needs an extensive insight and deep study which can be important tool in treating prostatic hyperplasia.

**KEYWORDS**

Prostatic Hyperplasia, Prostate, Mechanism of Action, Existing Treatment

**INTRODUCTION**

Prostatic hyperplasia is a noncancerous (benign) growth of the cells within the prostate gland. It is common in older men. Prostatic hyperplasia affects the inside part of the prostate first. Enlargement frequently causes a gradual squeezing of the urethra where it runs through the prostate. Sometimes this causes difficulty in urinating or other urinary problems. Prostatic hyperplasia is an enlargement of the prostate that is very common and leads to troublesome lower urinary tract symptoms (LUTS) in some

men. It is not the same as prostate cancer. Prostatic hyperplasia is a benign, non-cancerous enlargement. When physicians examine prostate tissue under the microscope, changes can be seen in about 25% of 40 year-old men and about 75% of 70 year-old men.

Having severe LUTS, or having an episode where a man is unable to urinate (urinary retention), or having a procedure to relieve symptoms, is higher for men with larger prostates. Although most men seek care for the symptoms of BPH, urinary tract obstruction due to longstanding BPH can cause some major health problems such as bleeding from the prostate, recurrent infections, bladder stones, inability to urinate, kidney insufficiency or

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kidney failure. Men with lower urinary tract symptoms due to BPH have many effective medications to relieve symptoms, slow the growth of their prostate and decrease the risk of future urinary difficulties. New procedures have decreased the risk of interventions to relieve obstruction. Traditional surgical therapies for prostatic hyperplasia such as transurethral resection of the prostate and with fewer surgical problems than in the past<sup>1</sup>

The prostate is divided into 2 separate parts-

The inner periurethral female part which is sensitive to estrogen and androgen

Outer sub capsular true male part which is sensitive to androgen.

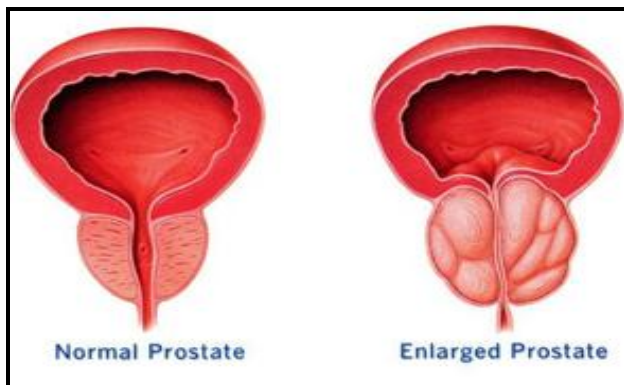


Figure 1: Difference between normal prostate and enlarged prostate.<sup>3</sup>

While benign nodular hyperplasia occurs in the periurethral part distorting and compressing the centrally located urethral lumen, the prostatic carcinoma usually arises from the outer subcapsular part in which case it does not compress the urethra<sup>2</sup>

### Mechanism of Prostatic Hyperplasia

Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator of prostatic growth. DHT is synthesized in the prostate from circulating testosterone by the action of the two types of isoenzyme 5 $\alpha$ -reductase. This enzyme is localized principally in the stromal cells; hence, those cells are the main site for the synthesis of DHT. DHT can act in an autocrine fashion on the stromal cells or in paracrine fashion by diffusing into nearby epithelial cells. In both of these cell

types, DHT binds to nuclear androgen receptor to form a DHT-androgen receptor complex and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells, which regulate cell division and proliferation in the prostate. DHT is 10 times more potent than testosterone because it dissociates from the androgen receptor more slowly. The importance of DHT in causing nodular hyperplasia is supported by clinical observations in which an inhibitor of 5 $\alpha$ -reductase is given to men with this condition. Therapy with 5 $\alpha$ -reductase inhibitor markedly reduces the DHT content of the prostate and, in turn, reduces prostate volume and, in many cases, hyperplastic symptoms<sup>4</sup>

Testosterone promotes prostate cell proliferation but relatively low levels of serum testosterone are found in patients with BPH. While there is some evidence that estrogen may play a role in the etiology of prostatic hyperplasia, this effect appears to be mediated mainly through local conversion of estrogen to androgens in the prostate tissue rather than a direct effect of estrogen itself.

### Treatment

- Watchful waiting (no treatment)
- Medical treatments (drugs)
- Minimally-Invasive Treatments
- Surgical treatment

### Watchful Waiting Treatment

This option is recommended as an important option for men who have mild symptoms and do not find them particularly bothersome. This means that he will be examined one or more times a year to make certain that you are not developing complications from prostatic hyperplasia.

As long as the symptoms are mild and not causing any change in the day-to-day activities, wait and watch approach with regular check-up is recommended. However, if the symptoms are troublesome, pharmacological treatment is recommended. And with potentially serious

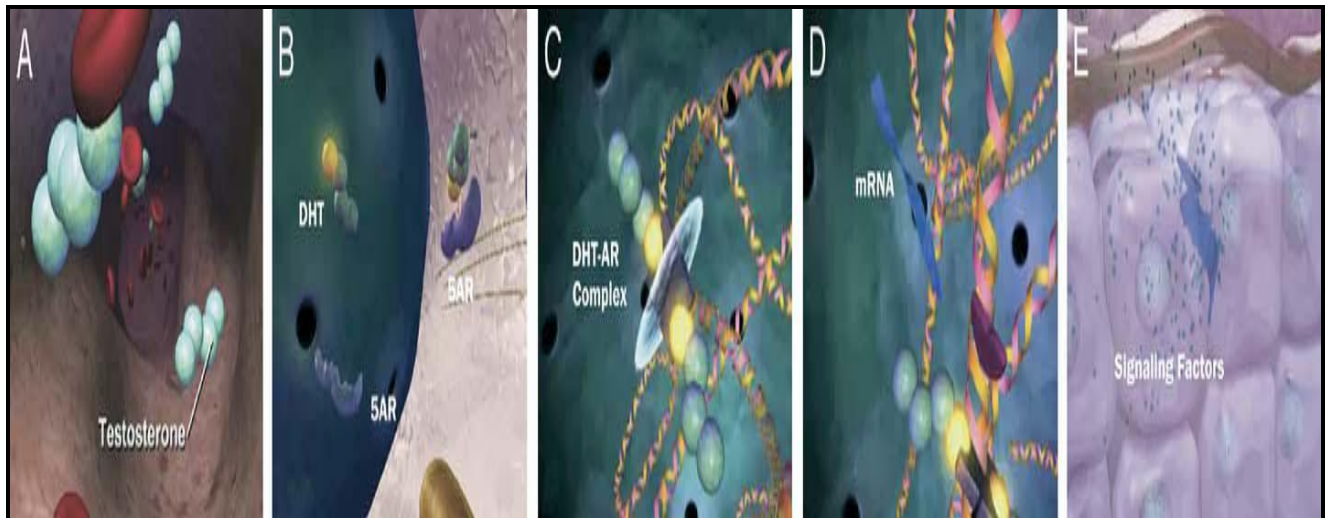


Figure 2: Prostate growth is regulated by androgens, particularly DHT. Testosterone is converted to DHT by 5AR isoenzyme types 1 and 2 (A and B). DHT binds to androgen receptor to form DHT-androgen receptor complex (C), which causes intracellular event cascade that leads to gene expression (D), and production of growth and signaling factors that regulate cell division and proliferation in prostate (E)<sup>5</sup>

symptoms, surgical interventions are considered.<sup>6</sup>

### Medical Therapy for LUTS and Prostatic Hyperplasia

Medical therapy for BPH can be roughly divided into following groups;

- Alternative therapies,
- Alpha-blockers and
- 5 alpha-reductase inhibitors

#### *Interventional Therapy*

This discussion will be fairly brief and not all-inclusive of potential risks and adverse events with the medications mentioned. The reader is referred to the Physicians Desk Reference or the medications package insert for detailed prescription information and potential adverse events.

#### *Alternative Therapies- Herbal Remedies*

For middle-aged men, painful urination can be an indication that they have developed prostatic hyperplasia. If diagnosed with this condition, there are herbal remedies that can help ease the severity of symptoms.

The healing garden offers several remedies for Prostatic hyperplasia. Tea, tincture, or capsules of hydrangea root or horsetail are often used to reduce the inflammation of the prostate gland. Nettle root tincture or capsules are also helpful. In fact, scientific studies have proved its ability to diminish this enlarged gland. Amounts used in successful studies range from 6-12 mL of tincture per day in divided doses, or 120 mg capsules twice a day.



Figure: 3 Pumpkin seeds are rich in the essential minerals zinc and copper

**Saw palmetto**, Saw Palmetto, extract of the berries of the dwarf palm tree of *S. repens* (family Arecaceae) is most widely used.<sup>7</sup>



provides great therapy for the enlarged prostate. In fact, one study showed significant improvement in 45 days with only mild or no side effects. However, saw palmetto is a wild palm tree that grows in swamps of the southeastern United States so it's not likely to be in your garden or landscape. For best results, use a combination of all the herbs mentioned. Since excessive consumption of animal products increases the risk of prostatic hyperplasia, eating more vegetables and fruits of all kinds is likely to be beneficial.

The mineral zinc may halt the processing of testosterone into DHT and thus may prevent or even reverse the condition. Pumpkin seeds from an excellent source of zinc, eating 2 ounces of pumpkin seeds per day significantly boosts zinc intake. Some people prefer to take zinc supplements. If someone decides to supplement with zinc, use no more than 50 mg per day for three months and include a copper supplement of 2 mg per day.

While some people may dismiss herbal remedies as quackery, the use of botanicals is well rooted in medical practice. Ancient doctors methodically collected information about herbs and developed well-defined pharmacopoeias to treat a variety of ailments. More than a quarter of all drugs used today contain active ingredients derived from those same ancient plants. The trail is carefully evaluating the effectiveness of saw palmetto for prostatic hyperplasia. The consensus of prior published data on saw palmetto is that it is likely safe and may be effective for some men with mild BPH symptoms.<sup>8</sup>

### ***Alpha-Blocker Therapy***<sup>9</sup>

The prostate capsule and bladder neck have alpha-adrenergic receptors. Alpha-blockers inhibit alpha-adrenergic receptors, causing relaxation of the prostate capsule, enhanced urethral opening and a stronger urinary stream with more complete bladder emptying. Alpha-blockers do not change the size of the prostate. The benefit of the medication is seen only as long as the patient takes the medication. Some of the medications in this class are also blood

pressure medications, while others have minimal effects on blood pressure. Generally long acting alpha-blockers are preferable for BPH treatment and the most commonly prescribed are

- Terazosin (Hytrin),
- Doxazosin (Cardura) and
- Tamsulosin (Flomax).

### ***Terazosin (Hytrin)***

Comes in 1, 2, 5 and 10 mg pills. It can sometimes cause lightheadedness or dizziness; therefore the dose is usually titrated or gradually increased until a therapeutic dose is reached. It is inexpensive and effective. Multiple randomized prospective placebo controlled studies have documented improved symptoms and urinary flow rate. Hytrin can cause blood pressure changes so patients on blood pressure medication may need their medicines adjusted by their physician.

### ***Doxazosin (Cardura)***

Comes in 1, 2, 4 and 8 mg pills. It can sometimes cause lightheadedness or dizziness; therefore the dose is usually titrated or gradually increased until a therapeutic dose is reached. It is inexpensive and effective. Multiple randomized prospective placebo controlled studies have documented improved symptoms and urinary flow rate. Cardura can cause blood pressure changes so patients on blood pressure medication may need their medicines adjusted by their physician.

### ***Tamsulosin (Flomax)***

Comes in 0.4 and 0.8 mg pills. Its dose does not need titrating and most patients use the 0.4 mg dose unless they are very large. It is more expensive than the other alpha-blockers currently available. No adjustments to other blood pressure medications are required. Also, the therapeutic dose is reached more quickly, so he may have quicker symptom improvement. Flomax can cause dizziness and some patients notice less ejaculation (retrograde ejaculation) while taking the medication.<sup>10</sup>

### **5-Alpha-Reductase Inhibitors**

A second type of medication partially shrinks the enlarged prostate by lowering the level of the major male hormone inside the prostate. There are two medications in this class, Finasteride (Proscar) and Dutasteride (Avodart).

5 alpha-reductase inhibitors block an important enzyme that converts the primary male hormone, testosterone, into the primary male hormone with prostate effects, dihydrotestosterone (DHT). As a result of this inhibition, a patient's overall testosterone level stays the same or increases up to 10%, but their intraprostatic DHT decrease by over 90%. This therapy causes the prostate to stop growing and shrink up to 15-20% over the first year of therapy. The process is fairly slow and most patients begin to notice an improvement in BPH symptoms 3-6 months after initiating therapy. 5 alpha-reductase inhibitors appear most effective in men with larger prostates, at least 40 ccs in size. Also, the larger the prostate, the greater the relative benefits of 5 alpha-reductase inhibitors.

#### ***Finasteride (Proscar)***

Comes in 5 mg tablets and is taken once daily. It is a very safe medicine. The most common side effect seen in 5-9% of patients is difficulty with erections. This tends to be less of a problem in patients who take the drug for over a year. One of the most important benefits of long term Proscar use is that it decreases the chance by over 50% that a patient with BPH will have urinary retention or need surgery

This was documented by the Proscar long-term efficacy and safety study (PLESS), a 4 year placebo controlled trial. Also, there is now evidence from the Prostate Cancer Prevention Trial (PCPT) that Proscar taken for 7 years may decrease prostate cancer risk by 25% in some patients. This is a new somewhat controversial finding, but it is exciting and will be studied in more randomized trials.<sup>11</sup>

#### ***Dutasteride (Avodart)***

This is a new drug in the 5 alpha-reductase inhibitors class that may be more potent and has a longer half-life than Proscar. It appears to

cause similar symptom improvement and prostate size reduction. Avodart is expected to have similar risk reduction effects including less urinary retention and eliminating the need for surgery. It has a similar side effect profile to Proscar, although it may cause changes in thyroid stimulating hormone (TSH).

Combination treatment with 5 alpha-reductase inhibitors and alpha-blockers is attractive since these therapies work through different mechanisms.<sup>12</sup> A recent double blind, placebo controlled multicenter trial compared placebo, doxazosin, finasteride, and a combination of doxazosin and finasteride in over 3,000 patients.<sup>20</sup> The patients were followed for over 5 years. The trial showed that combination therapy might be more effective than either therapy alone in decreasing symptom scores and improving urinary flow rate. The obvious drawback of combination therapy is the combined risk of adverse events, higher costs and the trouble of taking two medications<sup>13</sup>.

### **Interventional Therapy**

Surgical therapy, usually with TURP is recommended for patients with complications due to BPH such as urinary retention, bladder stones, kidney failure due to BPH or gross urinary tract bleeding. Most patients who come to require or desire interventional therapy have persistent symptoms in spite of medical therapy or side effects from medical therapy that are bothersome. There are now a number of different options for such patients with BPH. Each of the different procedures has its own nuances, risks benefits, expected outcomes and possible complications. Following is a brief review each of them,

#### **Transurethral Needle Ablation (TUNA)**

The procedure takes approximately an hour and most patients go home with a urethral catheter in place for 3-7 days. It is a simple and relatively inexpensive procedure which utilizes needle to deliver high-frequency radio waves to destroy the enlarged prostatic tissue. TUNA is a successful treatment for small-sized gland and it poses a low or no risk for incontinence and

impotence.<sup>14</sup> Most patients find the procedure simple, painless and effective.

### **Microwave Thermotherapy**

The prostate uses microwave energy to heat the prostate tissue using a probe in the urethra. Some of the early reports of microwave therapy showed some improvement in urinary symptoms but no improvement in urinary flow rate. Newer microwave devices heat the prostate more effectively resulting in improvements in urinary symptoms and flow rate. The procedure is office based, usually under local anesthesia and/or sedation. It takes 30-60 minutes, most men require urethral catheterization for 3-7 days following the procedure. Immediately after the procedure, before ultimate improvement, most patients have worse urinary frequency and urgency. The re-operation rate or the chance of requiring a TURP is approximately 20%. MT has been found to be safe and cost effective, with reasonable improvement in urine flow rate and minimal impairment on sexual function.<sup>15</sup>

### **Interstitial Laser or the Indigola laser system**

It is an interstitial thermotherapy technique, designed for office-based use, which heats the prostate tissue causing shrinkage of obstructive tissue and improved urinary symptoms. It requires post-procedure catheterization and is associated with initial irritative voiding, followed by subsequent improvement in symptoms and flow rate. . It has been found to be safe and effective technique, with significant improvement in urinary flow rates and symptoms. Short operative time, minimal blood loss and fluid absorption, decreased hospital stay, impotence rates, and bladder neck contractures are few of the advantages of laser prostatectomy over the TURP and other conventional techniques.<sup>16</sup>

### **Ethanol Injection Therapy**

Transurethral injection of absolute ethanol into the lateral lobes of prostate produces necrotic effect on prostatic tissues, leading to fibrosis and shrinkage. Significant improvement has been reported in AUA symptoms score. Continual research is going on to dilute negative

factors like urinary retention, pain, dysuria, and prolonged period of catheterization with the aim to deliver safe, effective, and economical potential treatment.<sup>17</sup> This technique requires catheterization for 2-7 days and patients have initial urinary frequency that improves over time. By one month after the procedure, patients have improved symptoms and urinary flow rate. There have been infrequent reports of bladder injury from alcohol injection and rare patients ultimately require TURP. Christopher Kane, MD and Katsuto Shinohara, MD are investigators on a multicenter trial at the Veterans Affairs Medical Center San Francisco, sponsored by American Medical Systems (AMS), evaluating alcohol injection therapy

### **Surgery**

The distinction between interventional therapies and surgery for Prostatic hyperplasia is now blurring. Some of the procedures typically classified as surgical therapy like transurethral resection of the prostate (TURP) and transurethral incision of the prostate (TUIP), are currently performed with brief hospitalizations, usually from 24-48 hours. Some interventional therapies such as TUNA, began as procedures done under general anesthesia in a hospital setting and are now safely performed in the clinic setting.

### **Transurethral Resection of the Prostate (TURP)**

It has been the “gold standard” for improvement of symptoms, urinary flow rate and complications due to BPH. It was pioneered in the early 1900’s but has evolved dramatically over the years. TURP is currently a less invasive procedure with less risk, a briefer hospitalization and better outcomes than 10 years ago. The procedure is usually performed under regional (spinal) anesthesia with the patient awake. A cystoscope, with video monitoring system, is passed into the patient’s urethra and bladder and the obstructing prostate tissue is removed. Bleeding is carefully controlled with electrocautery.<sup>18</sup> The procedure normally takes 30-60 minutes. A urethral catheter is placed at the end of the procedure



and the patient is generally kept in the hospital overnight. The next day, if there is minimal urinary bleeding, the urethral catheter is removed and in most cases the patient is able to void. He then goes home and takes about a week off of work, depending on the type of work he does. After surgery, blood in the urine is common and normally clears in a period of days although it may persist for as long as 1-2 weeks. Urinary flow rate usually improves by about 100% and IPSS (symptom score) generally improves by about 75%. The chance of needing a blood transfusion, which used to be about 5-10% after a TURP, is now under 1%. The chance of needing an additional procedure or repeat TURP within 5 years is only about 5%. Retrograde ejaculation (less semen) is common. A decrease in erections occurs in about 10% of patients. TURP is still the most effective form of therapy for patients with LUTS due to BPH or complications from BPH.

### Transurethral Incision of the Prostate (TUIP)

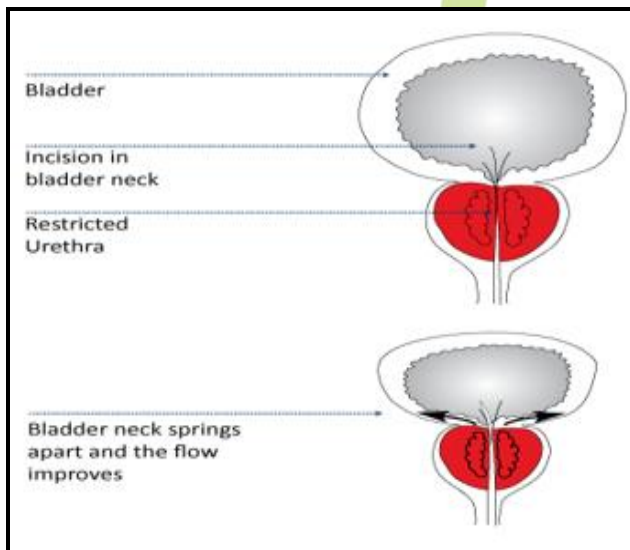


Figure: 4 Showing Transurethral Incision of the Prostate (TUIP)

It is a similar procedure to TURP, however instead of removing the obstructing tissue, an incision is made in the prostate lumen that allows the prostate lumen to open. The outcomes are similar to TURP for patients with prostates under 40 cc. With the exception that

retrograde ejaculation is less common, complications are similar to TURP.

### Open Prostatectomy

It is an open surgical procedure, usually undertaken in men who have very large prostates, over 100 ccs. Open prostatectomy is sometimes necessary because there is a practical limitation to how much tissue can be removed with TURP. The procedure requires spinal or general anesthesia and takes place through a lower abdominal incision. Surgery typically takes about 60-120 minutes to complete and requires a 2-4 day hospitalization. The urethral catheter is removed on the 3 to 5 postoperative day. Postoperative blood in the urine and retrograde ejaculation are common. The symptom improvement and improvement in urinary flow is similar to TURP.

### Photoselective Vaporization of the Prostate<sup>21</sup>

A prospective clinical trial was performed in 139 men clinically diagnosed with symptomatic bladder outlet obstruction secondary to BPH who were enrolled and treated with a high power, 80 W, quasicontinuous wave potassium-titanyl-phosphate laser at 6 American medical centers across the country. Efficacy parameters were mean and percent changes from baseline in the American Urological Association Symptom Index (AUA-SI) score, quality of life score (QOL), peak urinary flow rate (Qmax), post-void residual urine volume (PVR) and transrectal ultrasound prostate volume measurement. Patients were evaluated 1, 3, 6 and 12 months following treatment. At each follow up evaluation side effects were elicited.

### The Many Benefits of Photoselective Vaporization of the Prostate<sup>22</sup>

- Minimal bleeding
- Only 30% of patients need a post-op catheter
- Discharge on the same day
- Resume normal activities in 2 to 3 days with caution

- Return to vigorous activity level in 4 to 6 weeks
- Complications occur infrequently and are mild if they do
- Post-operative impotence has not been associated with PVP
- Retrograde ejaculation is less likely with PVP
- Erectile Dysfunction is not typical in PVP patients
- Long-term success in improved urine flow
- Fewer symptoms of urinary obstruction

## CONCLUSION

Prostatic Hyperplasia is the nonmalignant enlargement of the prostate gland and a common cause of voiding dysfunction in men. Watchful waiting is more appropriate for men with mild symptoms. Safe and effective treatment with 5 $\alpha$ -reductase inhibitors and  $\alpha$ 1AR antagonists can be achieved in patient with mild to moderate symptoms. Clinical efficacy of these agents has been further improved by using combination therapy; however, long-term outcomes of this study are still awaited. Traditional surgical treatment has been reported by TURP and minimally invasive techniques like hyperthermia and lasers.

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