PANEL DISCUSSION

Pelvic Pain of Venous Origin in Women

Key needs in clinical data, patient management, and awareness.

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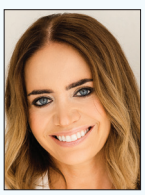

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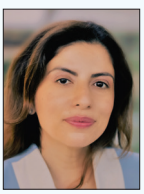

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Dr. Khilnani: Venous-origin female pelvic pain is often misdiagnosed or not considered, which results in many women being unsuccessfully treated for other possible causes. Identification of which symptoms and clinical signs might lead to earlier recognition of venous-origin chronic pelvic pain (VO-CPP)?

Dr. Jaworucka-Kaczorowska: VO-CPP, one of the clinical manifestations of pelvic venous disorder (PeVD), can be challenging to diagnose. CPP is a very common symptom with multiple potential etiologies and is often the result of an overlap of several pain-generating disorders of the reproductive tract and gastrointestinal (GI), urologic, musculoskeletal, and psychoneurologic systems. There is no consensus on the definition of CPP, but it generally refers to pain ≥ 6 months that occurs at the anatomic pelvis, anterior abdominal wall below the umbilicus, lumbosacral back, and buttocks and is severe enough to cause functional disability and requires treatment.[1] Early recognition and diagnosis of VO-CPP can be facilitated by identifying specific symptoms and clinical signs.

VO-CPP is often characterized as dull unilateral or bilateral pain with occasional sharp flares. Symptoms are often worse with activities such as walking and prolonged standing or sitting and improve with lying down, as this position helps reduce venous pressure. Pain can be constant, although it does not have to occur every day to be considered VO-CPP. It may follow a regular cycle, such as during menstruation (dysmenorrhea), during intercourse (dyspareunia), or as a postcoital pain.[1] Dysmenorrhea of the congestive type usually begins up to 1 week before menses (89%) and is described as low lateral and cramping. This is very similar to predysmenorrhea in endometriosis. Deep thrust dyspareunia and postcoital aching are found in 78% and 65%, respectively, of patients with PeVD. Although deep dyspareunia is common among women with pelvic pain from a variety of causes, VO-CPP is more likely to be associated with prolonged postcoital ache.[2] Patients with PeVD may also report a lower back pain, especially in the sacral area, which might be referred pain from the pelvis. The pain may also radiate down the legs, especially during menstruation. A characteristic feature of VO-CPP is that it is not relieved by analgesics.

Some patients report urinary symptoms, including frequency, urgency, or noninfectious dysuria or GI symptoms such as bloating or nausea. Patients may also exhibit symptoms related to orthostatic changes due to blood pooling in the pelvic veins.[3]

The presence of varicose veins in unusual locations such as the vulva, perineum, buttocks, or thighs may be helpful in identifying patients with PeVD; however, it should be emphasized that such patients usually do not have pelvic symptoms, as the venous hypertension is transmitted from the pelvis to a further zone through the pelvic escape points. VO-CPP has been observed in < 10% of patients with varicose vein of pelvic origin.[4,5]

It is essential to include VO-CPP in the differential diagnosis of women presenting with CPP, especially when other common causes have been ruled out or when the symptoms align with those described above.

Dr. Salazar: The major issue in properly diagnosing VO-CPP is the lack of a standardized patient-reported questionnaire for symptom assessment. However, VO-CPP is described as persistent, dull, unilateral or bilateral pain with occasional acute flares that can occur in the abdomen, back, or legs. Symptoms can worsen with activities such as walking or prolonged standing and are often relieved when lying down. Postcoital pain and dysmenorrhea are common concerns for patients and is reported in 40% to 76% of patients. In contrast to dyspareunia from endometriosis, which usually occurs with deep penetration, pelvic venous pain worsens during sexual intercourse but persists afterwards, manifesting as a throbbing ache by some reports. Adnexal tenderness is often reproducible on bimanual exam. In fact, the dual signs of postcoital ache and tenderness over the ovarian point on examination is 94% sensitive and 77% specific for distinguishing VO-CPP from other causes of pelvic pain.[6]

Dr. Khilnani: What are some of the more common misdiagnoses?

Dr. Winokur: Many alternative diagnoses of CPP can occur for a variety of reasons, with a high percentage originating from a nonvascular source. This can be easily worked up in the initial assessment of these patients to exclude endometriosis. When endometriosis is not identified and muscular pelvic floor dysfunction is not modifiable, dilated and overpressurized pelvic veins can lead to pelvic varices in the periuterine and periovarian spaces. Imaging workup of the patient with ultrasound and/or MRI as well as response to other treatment modalities such as pelvic floor physicial therapy will help guide if VO-CPP is the primary source requiring further management/intervention.

Dr. Jaworucka-Kaczorowska: Because symptoms of various pain-generating conditions are similar and multiple diseases frequently occur and trigger pain at the same time, it is often difficult to accurately diagnose the true cause of CPP, leading to misdiagnoses. The five most common misdiagnoses include gynecologic disorders known as chronic uterine pain disorders, irritable bowel syndrome (IBS), painful bladder syndrome, musculoskeletal pelvic floor pain, and peripheral neuropathy.[1]

Gynecologic disorders account for approximately 20% of cases of CPP, and endometriosis and adenomyosis are the most common.[7] The symptoms associated with these hormonally driven conditions include pain in the lower abdomen or pelvis, which varies markedly over the menstrual cycle, worsening during menstruation and preventing normal activities. It may also involve pain during or after intercourse, urination, and/or defecation; nausea; constipation; diarrhea; or blood in urine or stool, especially during periods, so the symptoms are very similar to pelvic symptoms of PeVD.[8] Other gynecologic disorders that should be considered in the differential diagnosis of CPP include adhesions, uterine fibroids, pelvic inflammatory disease, residual ovary syndrome, and ovarian tumors, although CPP is not a basic and characteristic symptom for these disorders.[1]

In a cohort analysis of a primary care database, IBS and interstitial cystitis (IC) were the most common diagnoses of women with CPP across all age groups.[7] These conditions may be a primary cause of CPP, a component of

CPP, or a secondary effect caused by efferent neurologic dysfunction in the presence of chronic pain. IBS is very often a comorbidity, with a high prevalence in women with endometriosis and other CPP-generating disorders, and may have a negative impact on the diagnostic and treatment process. The symptoms of PeVD, such as bloating, abdominal discomfort, and pain, can mimic IBS, also leading to misdiagnosis.

Recent data suggest that IC, characterized by chronic bladder and urinary urgency in the absence of an identifiable etiology, is one of the most common causes of CPP.[9,10] The most common symptom of IC is CPP localized in the suprapubic, pubic, vaginal, and genital areas. Some patients report unilateral lower abdominal pain or low back pain with bladder filling. Symptoms may be triggered or exacerbated by vaginal intercourse, exercise, or prolonged sitting; after intake of certain foods or drinks; during stress; or during the luteal phase of the menstrual cycle.[11] Patients with PeVD may experience similar CPP and bladder symptoms like frequency and urgency, which can be confused with IC.

Myofascial pelvic pain syndrome (MPPS) results from dysfunction, spasticity, and/or hypersensitivity of muscles, fascia, or joints in the abdominal wall, pelvic floor, and/or low back. This is an extremely common but underrecognized cause of CPP in women.[12] Pain related to MPPS involves the vulva, perineum, rectum, and bladder and more distant areas such as the thighs, buttocks, or lower abdomen. It may also influence urinary, bowel, and sexual function. Irritative symptoms, including vulvar or vaginal burning or itching, pain during or after intercourse, urinary urgency, frequency, and dysuria can be even more frequently reported than CPP.[13]

The entrapment of abdominal or pelvic nerves, such as iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, or pudendal nerves, may cause CPP in the anatomic distribution of this nerve, leading to misdiagnosis; therefore, it should be considered in the differential diagnosis of CPP.

Another difficulty in CPP diagnosis is that most patients with PeVD are asymptomatic.[5] It is still unknown which patients will develop symptoms and why, if the symptoms are related to PeVD, or if PeVD is only an asymptomatic comorbidity. Vein dilation and venous reflux is not enough to lead to both the symptoms and the diagnosis of PeVD. There are no validated criteria and cut points to diagnose this disorder. Incompetent and dilated ovarian veins can be found in almost 50% of asymptomatic women, as can pelvic varicose veins, especially after second pregnancy. Additionally, 90% of patients do not have valves in internal iliac veins (IIVs). Asymptomatic compression of the CIV and left renal vein (≥ 50% area reduction) may be present in 25% to 33% and 51% to 72% of the general population, respectively.[5]

An additional important aspect that often leads to misdiagnoses is central sensitization, which occurs when sensory pain information is abnormally processed, causing increased responsiveness in the central nervous system to either normal or sub-threshold afferent input. Central sensitization was found in 75% of 111 women with CPP in an observational, cross-sectional study.[14] Patients with central sensitization experience more prolonged and complex pain. This condition may hinder diagnostics and have a negative impact on the treatment outcome.

Because of multiple difficulties mentioned above, proper diagnosis of CPP requires a multidisciplinary approach involving gynecologists, interventional radiologists, vascular specialists, urologists, gastroenterologists, and pain specialists to differentiate between these conditions and provide appropriate treatment.

Dr. Khilnani: What are some of the essentials of a comprehensive physical exam to make a diagnosis?

Dr. Salazar: The clinical exam is extremely important to properly categorize patients for treatment planning. Adnexal tenderness at the ovarian point seems to be highly sensitive for VO-CPP but is not always present in patients with extrapelvic symptoms. It is imperative to evaluate for presence of gluteal and labial varices as well as signs of chronic venous disease (presence of leg varices, edema).

Dr. Jaworucka-Kaczorowska: In addition to a proper history taking—including questions about past pregnancies; location of pain and its quality, severity, and distribution; factors provoking or exacerbating pain and alleviating factors; and other gynecologic, urologic, GI, musculoskeletal, neurologic, and psychologic symptoms—a comprehensive physical examination is essential in the diagnostic process of VO-CPP.

Detailed examination should be performed in standing, sitting, supine, and lithotomy positions. During visual inspection, external genitalia and lower limbs should be checked for any signs and symptoms of PeVD, including varicose veins of pelvic origin or leg edema and venous leg ulcers potentially related to CIV compression.

Most helpful in the differential diagnosis of patients with CPP is bimanual examination. It starts from the single-digit examination of the pelvic floor. Palpation of the anterior vaginal wall, cervix, uterus, vaginal fornix, levator ani, internal transverse perineal, and obturator internus muscles allows assessment of contracted or

painful muscles and trigger points and helps identify patients with MPPS.[15] Bimanual examination can additionally help distinguish pain arising from the pelvic floor, urethra, bladder, uterus, and adnexa versus the abdominal wall. More diffuse uterine, adnexa, and parametrium tenderness as well as tenderness in the ovarian point (the junction of the upper and middle thirds of a line drawn from the umbilicus to the anterior superior iliac spine) with no pelvic floor tenderness is more suggestive of VO-CPP. In this case, uterine and adnexal palpation usually reproduces deep dyspareunia and palpation of ovarian point pelvic pain. The combination of postcoital ache and tenderness over the ovarian point during bimanual examination has been reported to be 94% sensitive and 77% specific for distinguishing between VO-CPP and other causes of pelvic pain.[2,3] A more recent study showed 87% sensitivity and only 37% specificity of ovarian point tenderness.[6]

Rectovaginal examination should be considered selectively for deep pelvic pain presentations to identify nodularity or tenderness in the rectovaginal septum or uterosacral ligaments, which may occur with deep infiltrating endometriosis. It allows to assess for rectovaginal mobility, as obliterative cul-de-sac endometriosis can cause tethering of the uterus and rectum.[16,17]

Dr. Khilnani: What do you look for on imaging?

Dr. Winokur: High-quality imaging of the pelvis is a critical component in the workup of women with CPP and typically worsening factors such as gravity or flow-stimulating activity. The ideal use of imaging will show dilated periuterine and periovarian veins associated with abnormal venous outflow such as to the ovarian veins and/or IIVs. Identifying dilation and reflux in the left and/or right ovarian vein is key to finding the source of pelvic venous hypertension leading to the periuterine varices that are most frequently associated with symptoms. It is also important to view the renal vein and CIV to exclude obstruction or postthrombotic change as the source of pelvic venous hypertension.

Dr. Salazar: Transvaginal ultrasound (TVUS) can help elucidate the diagnosis of PeVD and is a good imaging option for screening of patients. TVUS allows for identification of concurrent pelvic pathology (including fibroids), diameter measurement and qualitative estimate of the number of veins in the periuterine venous plexus, and assessment of flow during and after Valsalva maneuver with use of Doppler ultrasound. However, a comprehensive imaging workup must include ovarian, iliac, and escape point evaluation, ideally with physiologic maneuvers to detect reflux and evaluate presence of venous stenosis. An ultrasound protocol has been previously described, and more recently, a dedicated evaluation of pelvic escape points has been published.[18]

Dr. Khilnani: How would you summarize the challenges of nomenclature in female pelvic venous disorders, as well as recent efforts to clarify and develop more universally adopted terms?

Dr. Winokur: The naming of VO-CPP is a major challenge that is leading to updated use of terminology such as PeVD as opposed to pelvic congestion syndrome (PCS). The use of PCS often leads to absence of insurance coverage for the patient, and it is both important and helpful to use naming such as VO-CPP or PeVD. This naming is also very appropriate because it accounts for other causes of pelvic varices, such as iliac or renal vein obstruction leading to elevated pelvic venous pressure and CPP. Standard use of updated identifying terminology has the potential to improve coverage of intravascular procedures in this patient population, but upcoming randomized controlled trials (RCTs) of ovarian vein embolization (OVE) will be very necessary to advance the ability to prove its efficacy.

Dr. Khilnani: What are some of real-world challenges faced by patients and their doctors in terms of payment/reimbursement and access to care for treatments to palliate VO-CPP?

Dr. Salazar: The inability to identify a diagnosis leaves many patients with CPP frustrated, with suggestions that their problems are psychologic, and they often end up seeking advice from multiple physicians or withdrawing from further evaluation despite ongoing symptoms. This situation can even result into unnecessary treatments, including hysterectomy, without improvement in symptoms. Vascular specialists help elucidate the proper diagnosis of these patients that often are "lost in the medical system" and endure years of CPP secondary to pelvic varices.

Dr. Winokur: Real-world coverage of VO-CPP is not consistent in all cases. It appears that use of OVE for treatment of VO-CPP will continue to be a reimbursement challenge until we have RCT data to show efficacy of decreasing pelvic venous pressure through OVE and elimination of pelvic varices. The upcoming EMBOLIZE RCT sponsored by the Society of Interventional Radiology, VIVA Foundation, and Penumbra, Inc. evaluating outcomes of OVE will strongly help produce data we think will support the value of embolization for VO-CPP and justify payment/reimbursement for this treatment.

Dr. Khilnani: What are the current treatment options, and when do you choose one over another?

Dr. Winokur: The standard evaluation of this patient population incorporates imaging of the pelvis that can help in the assessment of the source of dilated pelvic varices. It is important to consider primary ovarian vein reflux, iliac vein obstruction, and renal vein obstruction as the potential sources of pelvic venous hypertension and/or varices. Although renal vein obstruction can be a cause of this, there are many cases of collateral formation preventing true impact on kidney function. Data from the EMBOLIZE trial may assist in understanding the true impact of renal vein compression and the impact of OVE on future renal function. EMBOLIZE will also help in delineating or staging of treatment for ovarian vein reflux and/or iliac vein obstruction, as patients will be primarily treated with OVE. It is important to allow for evolution in pelvic venous hypertension over time after OVE prior to iliac vein stent placement in most cases. This time point will become clearer following outcomes from the EMBOLIZE trial and initial pelvic venous embolization.

Dr. Jaworucka-Kaczorowska: Treatment options depend mainly on the pathophysiology but also on patient preference. The most common etiopathogenesis of VO-CPP is primary reflux, especially of the ovarian veins, and in this case, the treatment of choice is pelvic vein embolization.[5,19] There is no definitive treatment protocol. Both the technique of the procedure, including the site of endovascular access, and the materials used for embolization, such as coils, plugs, Gelfoam (Pfizer, Inc.), and liquids (sclerosants, Onyx [Medtronic], glue), vary in published articles. Studies comparing different embolization agents are still lacking, and their choice depends on physician preference.[20] The most commonly used are coils and foam sclerotherapy. In general, in patients with PeVD, OVE and/or IIV embolization have very good technical and clinical success rates with relatively low complication rates. Based on systematic review of 14 prospective studies, 68.3% to 100% patients reported some degree of symptomatic improvement, 0% to 31.7% reported no symptom change, and 0% to 4.1% reported worsening of symptoms following intervention. Of patients initially reporting symptom improvement, 0% to 18.2% noted symptom recurrence occurring over a range from 4 to 12 months.[21] In another systematic review involving 21 prospective case studies and one RCT, early substantial relief from pain was observed in 75% of women.[22]

When iliac vein stenosis is present, the goal of treatment is to remove the obstruction by percutaneous endovascular iliac vein stenting. Some studies report that iliac stenosis > 50% on intravascular ultrasound may be present in up to 80% of patients and that in patients with combined ovarian vein reflux and iliac vein outflow obstruction, pelvic venous outflow lesions should be treated first and ovarian vein reflux treated only if symptoms persist.[23] Complete resolution of symptoms after iliac vein stenting alone was achieved in 76% of women with PVI caused by iliac vein stenosis.[24] However, another study achieved resolution of symptoms in only 16.6% of patients after stenting of the left CIV without embolization of the gonadal veins. The combination of iliac vein stenting and gonadal vein embolization resulted in symptom relief in 83.4% of patients.[25] Further comparative studies are needed to determine the appropriate approach.

We can't forget about conservative treatment, especially in cases of mild or moderate symptoms when a patient does not want an invasive approach or has contraindications. It is also a useful option in patients with other comorbidities, especially endometriosis, and when the true etiology of CPP is unclear. Pharmacologic suppression of ovarian function may result in CPP relief and may be achieved using long-acting reversible contraceptives, medroxyprogesterone acetate, gonadotropin-releasing hormone agonists, and danazol. These have been proven to be effective in treating pelvic symptoms of PeVD. Venoactive drugs, such as micronized purified flavonoid fraction, have also provided improvements in CPP associated with PVI.[26]

Dr. Khilnani: What are your thoughts on some of the challenging procedural decisions, such as…

…Whether and when to do sclerotherapy of the reservoirs?

Dr. Winokur: I believe that it is critical to include sclerosant injection and treatment of the pelvic reservoir as part of complete OVE. If we look back at older data, many only performed coil embolization of a unilateral ovarian vein and did not include direct treatment of the pelvic reservoir. Those varices can then become a source that recruits retrograde flow from the untreated ovarian vein or potentially other venous networks that empty into the IIV. Although pelvic venous recurrence can occur after closure of a refluxing ovarian vein alone, absence of treatment to the pelvic reservoir, bilateral ovarian veins, or the varices directly can lead to recurrent pelvic varices similar to lower extremity varicose vein recurrence after treatment of a primary refluxing superficial vein such as the great saphenous vein.

…How many veins to embolize?

Dr. Winokur: It is important to perform complete embolization for success, defined as resorption of the entire pelvic reservoir. Injection of sclerosant or material to cause closure of the pelvic varices is important. It is also important to completely close the ovarian veins to prevent recurrent pressurization and filling of the pelvic reservoir. We will learn more from upcoming research about recurrence rates based on the number and location of venous intervention. The EMBOLIZE trial is directed toward complete treatment strategies of the entirety of the pelvic reservoir through direct injection of sclerosant into the varices from all identified sources and coil embolization/closure of the bilateral ovarian veins.

…How to handle the internal iliac reflux?

Dr. Salazar: Although some publications support the use of coils and plugs to embolize the IIVs, in our practice, we elect to use balloon occlusion sclerotherapy for the treatment of the IIV varices. A right femoral vein access is obtained via a 9-F short sheath and the contralateral IIV is selected with a 5-F Cobra catheter. A 5.5-F Fogarty occlusion balloon or 7-F Berman wedge catheter is exchanged over a 0.035-inch Rosen wire and placed just above the true pelvis where the tributaries and ovarian vein join. This is repeated on the contralateral side to select both IIVs. The volume of the pelvic varices venous plexus can be estimated by inflating the balloon and injecting contrast until normal veins are opacified. The volume of sclerosing agent should be 75% of the measured volume. We use a 3% sodium tetradecyl sulfate solution mixed with air at a 1:4 ratio to create a sclerosant foam. Once delivered into the varices, the balloons remain inflated for 5 minutes to prevent nontarget sclerosis. The embolization can be repeated on the contralateral side if necessary.

…How to manage patients with both reflux and iliac vein obstruction?

Dr. Salazar: The management of combined pattern of obstruction and reflux in patients with PeVD remains an area of active research. There have been case series reporting persistent symptoms after stenting alone requiring OVE in the long term, as well as studies suggesting that stenting alone should be sufficient. At this point, the choice of treatment algorithm depends on patient presentation and operator preference. Although the proper pathophysiology in these patients is still debated and given the lack of high-quality scientific evidence, staged OVE followed by stenting seems to be a reasonable approach, particularly in patients with significant venous stenosis. However, there are still concerns about long-term outcomes in younger patients, particularly in women of childbearing age. Future research should focus on individual trials evaluating patients with isolated ovarian vein reflux, iliac vein stenosis, and SVP (symptoms, varices, pathophysiology) S2 pelvic symptoms separately.

Dr. Khilnani: The EMBOLIZE RCT has recently begun, and several of you are leading the trial. In a big-picture sense, what do you hope to accomplish with EMBOLIZE?

Dr. Winokur: EMBOLIZE is a critical opportunity to prove the efficacy of complete embolization of the ovarian vein and the pelvic reservoir with a potential to impact insurance coverage as well as acceptance by all clinical specialties in the pelvic pain community. We need RCT data to prove efficacy of this type of treatment that will also hopefully change acceptance by the gynecology community to facilitate this treatment option in the affected patient population.

Dr. Salazar: We would like to answer the question of whether OVE and internal iliac reflux embolization does improve VO-CPP. This trial will allow us to take the first steps into bringing a higher scientific level to our research in PeVD.

Dr. Khilnani: How can public awareness of VO-CPP in women be enhanced? What are some modern approaches to ensuring patients and providers increasingly understand the condition and its potential treatment options?

Dr. Jaworucka-Kaczorowska: Enhancing awareness of VO-CPP among patients and health care providers requires a multifaceted approach involving education, digital technology, collaboration, and policy advocacy. It is important to cooperate with public health organizations and women's health advocacy groups to launch educational campaigns highlighting VO-CPP, its symptoms, diagnostic testing, and treatment options, including organizing workshops and seminars for both the public and health care providers. Raising awareness and providing comprehensive information about the disease can also be achieved or supported through a digital platform by holding webinars with experts in the field, which could be recorded and made widely available. It may also be helpful to create and maintain dedicated websites or online portals that offer detailed information on CPP and to use social media to disseminate information, share patient stories, and provide educational content on VO-CPP.

It is also important to establish networks or referral systems to connect primary care physicians with specialists who can diagnose and treat VO-CPP. Use of telemedicine can increase access to specialists, especially in underserved areas.

No less important is the promotion of research to better understand the condition and improve treatment options and the development of clinical guidelines to standardize care and ensure that providers are equipped with the necessary knowledge.

Dr. Salazar: Working to provide awareness to patients and support to vascular specialists treating these patients is crucial (eg, interventions such as education of primary care physician to provide proper referral of patients to vascular specialists), as well as improving the level of scientific evidence to enhance the quality of life of thousands of women around the world affected by PeVDs.

Dr. Winokur: The data from the EMBOLIZE trial will inform physicians in the relevant medical specialties evaluating and managing women with CPP. These data will be shared broadly and discussed with groups involved in female pelvic pain from multiple specialties; it is hoped that this will lead to reduced time to diagnosis and treatment of VO-CPP. ■

Disclosures

Dr. Khilnani: Speaker, Cook, Medtronic, Penumbra.
Dr. Jaworucka-Kaczorowska: None.
Dr. Salazar: Speaker's bureau, Medtronic, Boston Scientific Corporation, Cook, BD, Philips, Penumbra; advisory board, Medtronic and Boston Scientific Corporation; consultant to Medtronic, Boston Scientific Corporation, Cook, and BD.
Dr. Winokur: Consultant to BD/Bard, Cordis, Cook Medical, Inari Medical, Medtronic, Tactile Medical, and Penumbra.

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