Current Diagnosis and Treatment of Superficial Fibular Nerve Injuries and Entrapment

Peter J. Bregman, DPM, FAENS, Mark Schuenke, PhD

KEYWORDS
- Ankle
- Epineurium
- Leg
- Nerve sheath
- Neurolysis
- Nerve repair
- Neuroma

KEY POINTS
- Identification and treatment of entrapment of the SFN are important topics of discussion for foot and ankle surgeons, because overlooking the diagnosis can lead to permanent nerve damage.
- Some patients present with symptoms localized in their feet and, unless the examining clinician takes the time and makes the effort to look more proximal, the diagnosis may be missed if it is related to an SFN entrapment.
- Early diagnosis and treatment are crucial to avoidance of permanent nerve damage.
- Depending on the pathology, either decompression or, in cases of nerve trauma, neurectomy with implantation of the affected nerve into muscle with or without a nerve allograft is indicated. For this reason, peripheral nerve surgeons have to understand the rationale for and the technical maneuvers required to execute external neurolysis, nerve excision, and endoneurolysis, each of which is a fundamental element of basic peripheral nerve surgery.
- With the proper tools and skills, surgeons are able to help patients with symptomatic SFN entrapment, patients who often present in some degree of desperation, with the peripheral nerve surgeon as a last resort.

Financial Disclosures: None reported.
Conflict of Interest: Dr P.J. Bregman is a current member and past president of the Association of Extremity Nerve Surgeons. This is a nonprofit organization dedicated to the study of peripheral nerve disease and injuries to the lower extremity. The group is also involved in research and the teaching of peripheral nerve surgery.

E-mail address: drbregman@gmail.com
Much has been written on the diagnosis and treatment of superficial peroneal nerve (SPN) entrapment. The SPN is now known as the superficial fibular nerve (SFN). This article uses the abbreviation SFN to represent both. This commentary attempts to provide insight into this often misdiagnosed and certainly underdiagnosed lower extremity pathology. Some tips and pearls also are presented to aid in the diagnosis and treatment of SFN entrapment or injury. Some patients present with symptoms localized in their feet and, unless an examining clinician takes the time and makes the effort to look more proximal, the diagnosis may be missed if it is related to an SFN entrapment.

Depending on the pathology, either decompression or, in cases of nerve trauma, neuroectomy with implantation of the affected nerve into muscle with or without a nerve allograft is indicated. For this reason, peripheral nerve surgeons have to understand the rationale for and the technical maneuvers required to execute external neurolysis, nerve excision, and endoneurolysis, each of which is a fundamental element of basic peripheral nerve surgery. It is also important for surgeons to become skilled in the art of diagnostic blocks, to intimately know the anatomy of peripheral nerves in the lower extremity, and to identify and treat entrapment of the SFN (or any other named, anatomic nerve) inferior to the knee. With the proper tools and skills, surgeons are able to help patients with symptomatic SFN entrapment, patients who often present in some degree of desperation, with the peripheral nerve surgeon as a last resort.

To the authors’ knowledge, Kernohan and colleagues, in 1985, were the first to publish an article describing entrapment of the SFN, where they referred to Henry’s 1945 publication, entitled “Extensile Approach.” Styf, in 1989, stated that the incidence of SFN entrapment causing anterior lateral leg pain was probably higher than suggested in the literature at that time. Donovan and colleagues also stated that entrapment neuropathies of the knee, leg, ankle, and foot were often underdiagnosed, because clinical and electrodiagnostic evaluation was not always reliable. The nomenclature of the SPN has gradually become to be known as the SFN. This change in nomenclature was made by the anatomists and more or less has been adopted by most investigators.

A patient with peripheral nerve pathology can be treated surgically or nonsurgically, depending on the specific diagnosis, and appropriate surgical management may involve a neuroectomy or a decompression of 1 or more nerves. There are a variety of conservative treatment options, of which nerve gliding or nerve flossing (another term for nerve gliding) is the most commonly used and most effective. This involves specific maneuvers usually performed by a physical therapist that places a stretch on the entrapped nerve and also involves techniques to break up any adhesions of the surrounding fascia or scar tissue. The patient is given a specific home exercise program that incorporates these specific techniques. The concept of decompression of a peripheral nerve, and not those localized to the lower extremity, still seems controversial. The peer-reviewed literature pertaining to nerve entrapment of the upper extremity is voluminous. As the population becomes more obese and the diagnosis of diabetes mellitus more prevalent, symptomatic peripheral nerve conditions will concomitantly increase in frequency, and timely and accurate diagnosis and subsequent treatment of these peripheral nerve entrapments have become ever more important because a delay in treatment can lead to permanent nerve damage. Donovan and colleagues stated that if the symptoms of nerve entrapment persist for 2 to 3 months, then surgical decompression is usually required to prevent permanent nerve damage. This statement accentuates the importance of early diagnosis and early intervention. This also reinforces the idea that clinicians using nonsurgical...
techniques should be careful so as to avoid prolonged efforts that are not showing adequate results, again because permanent damage to the nerve could be present. Clinicians should be monitoring the progress of any treatment whether it is surgical or nonsurgical. This is accomplished by using 2-point discrimination, pinprick test, Pressure Specified Sensory Device (PSSD), and electrodiagnostic testing. The subjective data from a patient, such as pain relief and restoration of sensation, are also a way to document improvement. Improvement in the Tinel sign as well function of the nerve involved can be looked for. The PSSD machine is a valuable tool to monitor nerve healing. The PSSD machine provides 1-point and 2-point pressure and discrimination values that can be tracked. If there is not more than 10% improvement in the sensation of the affected nerve and no significant pain relief with 3 months of conservative therapy, then surgery should be considered. Every patient is different and other medical issues may influence the decision to proceed with surgery or continue with conservative therapy. The use of sclerosing alcohol injections and cryotherapy are intended to destroy nerve tissue and, once this has been done, ongoing treatment is limited to further destructive techniques. Looking at the typical treatment of an intermetatarsal nerve entrapment, where patients may receive a series of alcohol injections or steroids, these patients often go on to have a neurectomy, which is mostly successful but, when not successful, can lead to a stump neuroma with terrible consequences that require a much more involved treatment plan usually involving surgery of the plantar arch of the foot. It is the experience of one of the authors (PJB) that, in most cases, decompression is the preferred treatment over any destructive nerve procedure when there is no evidence of any true nerve injury.

The genesis of this author’s (PJB’s) interest in the diagnosis and treatment of SFN entrapment evolved from seeing certain patients with foot pain that was difficult to successfully treat. As an example, a patient presents with generalized lateral column pain or dorsolateral foot pain. It was usually exacerbated by squeezing the foot from side to side and bothered the patient with ambulation. The patient had symptoms localized to the dorsolateral aspect of the foot, as a result of entrapment of 1 of the branches of the SFN, which had a separate fascial sheath between the anterior and lateral compartments, which was alleviated by means of external neurolysis. This was reported by Rosson and Dellon in 2005.5

This commentary focuses on the entrapment of the SFN. The author (PJB) has operated on 35 cases of SFN entrapment over the past 4 years, with duration of follow-up of at least 1 year. At the authors’ center, close track is kept of the results of each particular nerve condition and the results of the interventions. Successful surgical intervention is defined as a 50% decrease in subjective pain, as defined in the Visual Analog Scale 10-cm pain scale, combined with patient indication that if the symptoms were the same, the patient would undergo the same surgery again. The current incidence of success is 92% over a 4-year observation period. The purpose of this commentary is to inform readers about this pathology and for them to be able diagnose this often overlooked nerve pathology and provide appropriate treatment or proper referral to a peripheral nerve specialist. It is important not to undertake any peripheral nerve surgery without proper training and experience.

ANATOMY OF THE SUPERFICIAL FIBULAR NERVE

The SFN supplies motor innervation to the fibularis longus and fibularis brevis muscles as well as cutaneous innervation to the anteroinferior portion of the leg and much of dorsum of the foot and toes. The SFN emerges as a terminal branch at the bifurcation of the common fibular nerve in the popliteal fossa, near the fibular head. After
supplying the fibularis musculature, the SFN typically passes inferiorly in the lateral leg, between the fibularis longus and the anterior crural intermuscular septum. In 23% to 27% of the population, the SFN may travel in the anterior compartment of the leg rather than the lateral compartment. In this case, the SFN may also provide muscular branches to the extensor hallucis longus muscle. Approximately 7.7 cm from the intermalleolar line, the SFN passes between the fibularis longus and the extensor digitorum longus and pierces the crural fascia. There is variability in where it becomes superficial through the fascia. The SFN then splits into a medial dorsal cutaneous nerve (MDCN) and an intermediate dorsal cutaneous nerve (IDCN); a lateral dorsal cutaneous nerve also exists as a branch from the sural nerve. In approximately 28% of the population, the SFN may split into terminal branches while still deep to the crural fascia. In this case, the MDCN typically emerges from the crural fascia, approximately 8.1 cm proximal to the intermalleolar line, whereas the IDCN emerges 2.6 cm more distally. Regardless of its point of emergence, the MDCN crosses anterior to the talocrural joint, equidistant from the medial and lateral malleoli, and bifurcates into dorsal digital nerves, supplying parts of digits 1 to 3. The IDCN also crosses the anterior of the talocrural joint at approximately one-third the distance from the lateral malleolus to the medial malleolus and branches to provide dorsal branches to digits 3 to 5 as well as a cutaneous branch to the lateral malleolus. In rare instances, the MDCN or IDCN may be absent. When this occurs, branches of the saphenous or sural nerves cover the cutaneous innervation, respectively.

It is important to appreciate the variable course of the SFN and its branches for the purpose of graft harvesting and to avoid iatrogenic injury. The MDCN and IDCN are endangered during the creation of anterolateral ports for arthroscopic procedures. Because the common site of anterolateral portal placement is along the lateral border of the fibularis tertius tendon or extensor digitorum longus tendon, the IDCN is at greater risk. To minimize the risk of damage, it may be possible to visualize the SFN and its terminal branches. In some patients, the SFN is visible on plantar flexion (approximately 10°) and inversion. As the foot is moved from plantarflexion, through neutral, and into dorsiflexion (approximately 5°), the SFN and its terminal branches displace laterally by a few millimeters. Visualization of the SFN is further accentuated by flexion of the fourth digit, and transillumination may also enhance visualization. Alternatively, the course of the SFN can be traced with ultrasonography if needed.

**DIAGNOSIS OF SUPERFICIAL FIBULAR NERVE ENTRAPMENT**

How can the correct diagnosis of an SFN injury or entrapment be made? Making a correct diagnosis of SFN pathology can be a difficult task. The symptoms tend to mimic other diagnoses but a thorough history and examination point surgeons in the right direction. Initially many patients with this type of nerve pain have sustained a traumatic injury to the lower leg, ankle, or foot that directly crushes, stretches, or tears the nerve trunk at the site of injury or additionally at a more proximal or distal location. If the mechanical force of this particular injury was sufficient enough to stretch or tear ankle ligaments, muscles, or tendons; fracture the fibula and/or tibia; or tear the syndesmotic ankle ligament, then there was more than enough energy to damage the relatively unprotected peripheral nerve(s). This injury could have occurred months or years prior to a patient seeking professional care, so it is important to document any trauma as far back as possible.

A patient’s occupation can also play a role in making the diagnosis. For example, dancers who frequently plantarflex and invert their ankle, in particular ballerinas en pointe, are prone to SFN entrapment and injury. Most prevalently, the common
inversion ankle sprain (contraction) or contusion to the anterolateral aspect of the leg blunt compression is responsible for entrapment of the SFN and/or its branches. The inversion injury involves high-velocity, rapid stretching of the nerve trunk in the leg where it emerges through the fascia (often referred to as Henry’s hiatus) as it exits the muscle compartment through the deep fascia. At this level, there can be direct trauma to the more distal divisions of the medial and IDCNs, traversing distally over the anterior lateral ankle and dorsal foot surfaces. Direct contusion to SFN trunk occurs most typically in athletes involved in field sports, such as soccer, field hockey, lacrosse, and football. Frequently, in softball and volleyball, players are injured when the ball strikes the lateral leg, resulting in contusion, disruption in the fascia, and herniation of the nerve into the subcutaneous layer (Fig. 2). It is also common to see these injuries in martial arts at any level of competition or training.

Anatomic anomaly, such as muscle herniation, can also result in or predispose to SFN entrapment and this condition was described by Yang, who reported successful treatment of the entrapment with external neurolysis and treatment. Seddon type 1 stretch injuries (without neural tear) represent more than 95% of this injury pattern and Seddon type 2 partial tear injuries are less than 5% that are clinically encountered. As can be seen, the SFN or its branches are vulnerable to injury in association with surgical repair of ruptured ankle ligaments, peroneal tendons, fixation of fibular fractures, and ankle arthroscopy using trocars placed through soft tissue portals. Chronic
postinjury inflammatory changes, which can develop in response to a wide range of pathologies, such as blunt or sectioning injuries, hematoma, cast immobilization, connective tissue disease, or infection, can lead to the formation of adhesions that entrap the SFN trunk in its adjacent soft tissues.

Clinical examination of a patient with a suspected SFN problem entails the typical elements of lower extremity sensory and motor testing, including assessment of 2-point discrimination, vibratory sensation, monofilamentesthesiometer sensation, manual muscle strength testing, assessment of deep tendon reflexes at the Achilles and patellar levels, superficial reflex assessment, and evaluation of the straight leg raise test and slump test. Focal palpation and manipulation of the suspected nerve trunk, with identification of a positive or negative Tinel sign, is also documented.

The use of diagnostic ultrasound enables visually identifying the nerves in the compartments of the leg. MRI neurography has allowed seeing areas of compression along the course of the entire peripheral nerve (although it is expensive and has limited availability). Once damage to the SFN and/or its branches is suspected, the authors advise systematically isolating the nerve and mark this out in the patient chart, noting the exact location of the most painful site as well as any Tinel sign and the distribution of radiation of the sign. For example, documenting can be as follows: Tinel’s sign 12 cm proximal to fibular malleolus and 2 cm lateral to tibial spine with radiation to the fourth metatarsal. The next step is performing diagnostic (and therapeutic) nerve blocks using only small amounts of lidocaine to attempt to temporarily relieve the patient of symptoms. It is important to know the anatomy when doing blocks so the responses can be interpreted. Individual responses to these diagnostic blocks need to be correlated with a physician’s knowledge of the variations in SFN branch patterns to develop a proper diagnosis. This helps determine if there are anatomic variations of the SFN present or additional peripheral sensory nerves that are involved.

Regarding peripheral nerve blockade with the use of a local anesthetic agent, it is important to note the position in the leg; the nerve may be deep or superficial to the crural fascia and the patient may need to be injected twice, with documentation of each response in the patient chart. The first injection is infiltrated in the subcutaneous tissue and if the patient does not describe greater than 75% relief after a few minutes, then a second injection result is given deep to the deep fascia layer. Placement of this second injection can be aided by ultrasound guidance. Once the documentation of the second injection results is complete, the appropriate treatment is determined. It may
be helpful to repeat the diagnostic nerve block on another visit to confirm the response to the injection and to better allow the patient to understand what can be anticipated should surgery be undertaken. After blockade of the SFN, extensive sensory anesthesia, as well as autonomic moor dysfunction, should be observed. If the first web space is spared and the patient’s symptoms are adequately relieved, then it is unlikely that the deep peroneal nerve is involved in any of the patient’s symptoms. It is also important to determine whether or not peripheral neuropathy (polyneuritis) is present and to distinguish it from a localized peripheral nerve entrapment (mononeuritis). This distinction can be made in several ways, including the use of a PSSD machine\textsuperscript{16} or, if that is not available, then a 2-point tactile discriminator (Fig. 3) suffices.

**SURGICAL DECOMPRESSION OF THE SUPERFICIAL FIBULAR NERVE**

After determining via diagnostic blocks and clinical examination that there is an entrapment of 1 or more branches of the SFN, then it should first be explained to the patient that the success rate of the decompression is approximately 85\%\textsuperscript{17–19} if diagnosed correctly. The authors believe that it is important to explain to patients that every person does not have the same “peripheral nerve anatomy” and that even though the diagnostic block and the subsequent surgical decompression were indicated and properly executed, it is possible that other peripheral nerves contribute to the symptoms and that this contribution by another nerve or nerves could be unmasked by the surgery may require further surgery. Preoperative documentation should be made of a patient’s maximum point of pain and Tinel sign as well as the distribution of the Tinel sign, because these are the strongest indicators of the specific nerve that requires decompression. When tapped percutaneously, the patient experiences pain and/or parasthesias at the site of percussion or usually distally in the anatomic distribution of the nerve. Sometimes the parasthesias radiates in the area of another named nerve, which can be confusing, and indicates a possible anatomic anomaly. Knowledge of the location of the Tinel sign enables surgeons to localize the incision over the most likely area of entrapment (Fig. 4). The authors have also found that perioperative use of drugs, such as gabapentin, desipramine, topiramate, vitamin C, and topical analgesic compounds, can be useful. These medications not only help patients prior to the decision to operate but also help during the recovery process, and in some patients these medications are continued indefinitely.

![Fig. 3. Diagram of 2-point discriminator. (Courtesy of US Neurologicals, LLC, Poulsbo, WA; with permission.)](image)
On the day of the surgery, the patient can be met in the preoperative holding area and the area to be decompressed confirmed and marked. Video 1 shows the decompression of the nerve with use of amniotic tissue graft.

The patient is then taken to the operating room and placed on the operating table in the supine position; a well-padded thigh tourniquet is applied at the surgeon’s discretion. The surgery could be performed with or without use of tourniquet hemostasis. If using a thigh tourniquet, then it is strongly encouraged to use general anesthesia because any tourniquet time of more than 20 minutes starts to cause painful ischemia and requires more anesthesia. The surgery can also be done easily with a spinal anesthesia without the side effects or risks of general anesthesia. Intravenous sedation is another choice but it is the authors’ (PJB’s) preference to avoid it because the other options are better tolerated. A superficial local anesthetic block is used to anesthetize the area of the planned dissection and in this case it is where the SFN emerges through the deep fascia and becomes subcutaneous. It is important to avoid excessive volume of local anesthetic so as not to obliterate the underlying anatomy. Bipolar cautery is used to coagulate any small vessels as well as fascia. Careful skin retraction is carried out using double skin hooks and meticulous tissue handling is always observed. To adequately decompress the SFN, the author (PJB) prefers a lazy-S type of incision, approximately 5 cm to 6 cm in length, although this can be extended at the surgeon’s discretion and 2 or 3 smaller incisions can be made to provide a more thorough decompression if needed. After opening the skin, sharp and blunt dissection methods using tenotomy scissors as well as diligent use of a wet sponge to help spread the adipose tissue are applied. The nerve(s) usually are encountered below the crural fascia at this level, although it is certainly possible to encounter a branch or 2 in the subcutaneous layer. Usually tendon and nerve can be seen through the crural fascia and these structures can guide the placement of the deep incision. A #15 blade is then used to perforate the deep/crural fascia after which the crural fascia is incised along the course of the nerve to expose it. Bipolar cautery is used to cauterize the margins of the deep fascia to avoid postoperative scar complications, because the fascia is a source of scar tissue that could adhere to the decompressed nerve trunk. After incising the crural fascia, access is gained to both the lateral (peroneal) and anterior muscle compartments of the leg; then careful inspection is carried to identify the SFB and all its branches. It is important to look with in the septum between the 2 compartments because a branch of the nerve can be located there as well (Fig. 5); this

![Fig. 4. Typical 6-cm incision to allow access to the SFN in the anterior and lateral compartment of the leg. It is centered approximately 11 cm to 12 cm above the ankle joint.](image-url)
The maneuver is demonstrated in Video 1, which displays a patient who had the SFN entrapped within a separate fascial tunnel in the anterior compartment of the leg. The fundamental maneuver required to effectively decompress the SFN and its branches is external neurolysis, and it is important to dissect both proximal and distal along the course of the nerve(s) until the trunks are no longer visually compressed. It is helpful to have an assistant use a deep retractor to elevate the skin so that the surgeon can look down the tunnel and make sure that no gross visual entrapment persists. Distally, the surgeon should be able to see the nerve split into the IDCN and the MDCN as they course toward the foot. Once all of the branches have been inspected and freed from any entrapment, any tissue that could produce scar tissue is electrocauterized with the bipolar unit after which copious lavage is performed (Fig. 6). Opening the anterior and lateral compartments is essentially performing fasciotomies of the respective compartments. This is especially important in the clinical setting of exercised induced chronic compartment syndrome. After SFN decompression and wound lavage, a cocktail of local anesthetic and dexamethasone phosphate is used to bathe the exposed nerve trunk to prolong local anesthesia and diminish immediate inflammation and fibroproliferation. This advised unless using any biologics, such as amniotic tissue graft or fluid (which is the author’s [PJB’s] preferred choice). If a tourniquet was used and there are any doubts about hemostasis, the tourniquet should be deflated prior to closure. Closure of the wound does not include the reapproximation of the crural fascia. The subcutaneous tissue is reapproximated with a few 4-0 poliglecaprone 25 sutures just enough to keep tension off the skin. The skin is closed with suture of surgeon’s choice and a Jones compression dressing is applied.

After the operation, the patient is encouraged to move the toes and ankle as much as desired while keeping the leg elevated for the first 48 hours. It is generally inappropriate to immobilize any extremity after any decompression of an in-continuity nerve trunk. The patient can walk up to 30 to 40 feet per hour for the first week then double that for the second week. The patient can walk as much as can be tolerated after 3 weeks as long as there is no significant swelling. Postoperative physical therapy is used as soon as possible after the first week, and aqua therapy is recommended after the skin sutures have been removed approximately 2 to 3 weeks after surgery. Nerve gliding techniques can also be helpful and should be instituted as soon as possible. It typically takes up to 4 to 6 weeks after the surgery before the patient can resume full activity without restrictions.
Achieving a successful outcome is predicated on performing the correct surgery and setting expectations accordingly. The generally accepted incidence of success after decompression of an in-continuity SFN trunk is approximately 85%.17–20 The definition of success must also be discussed with each patient. Many factors come into play, including but not limited to chronic use of pain medication, past medical history, history of depression, history of injury, smoking history, and patient’s desired functional level, to name a few. Failure of any decompression should be looked at closely and the surgeon needs to evaluate carefully why the surgery may have failed. The longer a patient has had the condition then the less likely the chance of a positive outcome. It is also important to determine if there are any other peripheral nerve contributions to a patient’s pain that may have been missed, including more proximal pathology, such as lumbosacral pathology. Any central nervous system issues also must be ruled out, especially a patient who may have centralized nerve pain. In cases of chronic nerve pain, the peripheral nerve problem can become centralized and this needs to be handled in a much different manner and requires a multifaceted approach. In cases of the SFN, the sural nerve may be contributing a branch or even be the source of the problem. It is important to make clear to patients preoperatively that everyone is not neurologically wired the same. The analogy of a house that was wired back in the 1960s works well when discussing variation in nerve distribution. An electrician assessing the house without being able to see the specific mechanical blueprints may have an idea of how things are wired but would not actually know until physically inspecting the actual wires. This analogy is helpful in explaining the surgery.
and its possible outcomes prior to undertaking decompression of the SFN. As discussed previously, reasons that these types of surgeries can fail is if the pain has become centralized, as is the case in many patients with chronic pain. In these cases, comanagement with a pain management specialist is required and the care of an experienced biopsychologist can be beneficial. The incidence of surgical success after decompression dramatically decreases in the face of centralized pain. Another facet of managing a patient with nerve pain is perioperative management. Still further, and as discussed previously, adjunct use of medications, such as gabapentin and topical analgesic compounds, can be useful in the preoperative and postoperative decompression period. Overall, a team approach to the peripheral nerve patient provides patients with the highest degree of success. This team includes anesthesia, pain management, psychology, physical therapy, and the surgeon. With proper training and experience, peripheral nerve surgeons can make an accurate and timely diagnosis and properly execute external neurolysis and successful decompression of the SFN (or any other nerve in the lower extremity).

In summary, the author (PJB) has commented on the approach to identification and treatment of entrapment of the SFN. This is an important topic of discussion for foot and ankle surgeons, because overlooking the diagnosis can lead to permanent nerve damage. The aim is to inform the readers of this pathology and remind them to consider it and not overlook the possibility of this condition as a cause of foot and ankle symptomology, because early diagnosis and treatment are, in the opinion of the author (PJB), crucial to avoidance of permanent nerve damage. Not every foot and ankle surgeon is interested in undertaking peripheral nerve surgery, and appropriate referral to a surgeon who specializes in treatment of the peripheral nerve can be helpful in making the proper diagnosis and receiving appropriate care, nonsurgical or otherwise. The Association of Extremity Nerve Surgeons has published guidelines on the diagnosis and treatment of peripheral nerve problems in the lower extremity, which readers can use as a reference and which can be found on their Web site: www.AENS.US.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cpm.2015.12.007.

REFERENCES