Complex Regional Pain Syndrome

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Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy, is a regional, posttraumatic, neuropathic pain problem that most often affects 1 or more limbs. Weir Mitchell identified a pattern of clinical signs and symptoms in Civil War casualties and first described CRPS in the 1860s. He used the term causalgia to describe the key feature of burning pain after penetrating limb injuries. The ensuing severe chronic pain was noted to be more prevalent when the limb injury involved a major peripheral nerve.

The nosology and terminology of posttraumatic limb pain have undergone a series of changes that have led to considerable confusion and controversy regarding the diagnosis and treatment of CRPS. Historically, CRPS has been known as RSD, posttraumatic dystrophy, causalgia, minor causalgia, Sudek atrophy, and shoulder-hand syndrome. The most popular contemporary label is RSD, and this terminology is based on the notion that a pathologic sympathetically maintained reflex arc is involved in the generation and perpetuation of pain. This theory was strengthened by anecdotal reports of relief after local anesthetic or pharmacological sympathetic ganglion blockade. Recent studies have shown that the sympathetic nervous system is not necessarily involved in every case and that a “reflex arc” has not been demonstrated.

To bring some order and uniformity to this problem, most pain experts now adhere to the terminology developed by an International Consensus Conference. Complex regional pain syndrome is used to describe a wide variety of posttraumatic neuropathic pain conditions, and CRPS has been subdivided into type 1 and type 2. The clinical features of the 2 types are identical. The distinguishing feature is the presence of a major peripheral nerve injury in patients with type 2. Diagnostic criteria for CRPS types 1 and 2 are listed in Table 1.

DIAGNOSIS
No specific test is available for CRPS, and no pathognomonic clinical feature identifies this condition. Rather, identifying a constellation of history, clinical examination, and supporting laboratory findings make the diagnosis. Complex regional pain syndrome can occur in children and adults.

CLINICAL HISTORY AND PHYSICAL EXAMINATION FINDINGS
Most patients with CRPS have an identifiable inciting or initiating injury, which may be trivial, such as a minor limb sprain, or severe, such as trauma involving a major nerve or nerves. The key features are pain, allodynia and hyperalgesia, abnormal vasomotor activity, and abnormal sudomotor activity persisting beyond the period of normal healing. Allodynia is defined as a disproportionally increased pain response to a nonnoxious stimulus. Hyperalgesia is defined as a disproportionately increased pain response to a mildly
noxious stimulus. The most common symptom is burning pain. Additional pain descriptors include throbbing, squeezing, aching, and shooting. The pain usually spreads beyond the area of the initial injury and in its most severe form may involve the entire limb and, rarely, the contralateral limb. Allodynia is usually present in addition to the ongoing spontaneous pain. Allodynia may be more troublesome than the spontaneous pain, and physical therapeutics are difficult or impossible to implement unless it is relieved. Occasionally, hyperpathia is seen, characterized by a disproportionately increased pain response to a stimulus, especially a repetitive stimulus, and an increased threshold.

Patients with CRPS often adopt a protective posture to guard the affected extremity from allodynia. They may wear a glove or stocking to protect the affected extremity from mechanical and thermal stimulation. Allodynia may be so severe that the patient will not allow the physician or therapist to examine or even touch the affected limb.

Symptoms of sympathetic dysfunction may be present and may manifest as vasomotor and/or sudomotor instability in the affected limb. These symptoms typically wax and wane and in later stages may not be present at the time of the initial examination. The typical signs are color changes, temperature changes, and excessive sweating. The patient may report that the extremity is warm and red or cool and dusky or mottled, and these symptoms are more prominent in the distal portion of the limb. Hyperhidrosis is a common finding early in the course of CRPS. Additional symptoms include joint swelling and stiffness, dystonic movements and posturing, and muscular weakness. Pain may accompany the sympathetic dysfunction, and if pain is relieved by sympathetic blockade, it is regarded as sympathetically maintained. Pain that is not relieved by sympathetic blockade is known as sympathetically independent pain. Also, pain that is sympathetically maintained can convert to sympathetically independent pain during the course of CRPS. The 2 types of pain frequently coexist, and our experience is that isolated, “pure” sympathetically maintained pain is rare.

Trophic changes of the affected limb may occur later in the course of CRPS. Nails may be hypertrophic or atrophic, hair growth and texture may be increased or decreased, and the skin may become atrophic. Motor dysfunction may be reported and may include tremor, dystonia, muscle spasms, and loss of strength and endurance of the affected muscle groups. Patients who have had symptoms for months to years may have severe brawny edema, muscle atrophy and contractures, and marked cyanosis of the limb. Treatment at this late stage is often unsuccessful.

The associated pain and disability may impair the patient’s ability to perform the necessary rehabilitation and normal vocational and self-care activities. This can lead to considerable anxiety regarding employment, financial ca-

Table 1. Diagnostic Criteria for Complex Regional Pain Syndrome Types 1 and 2

<table>
<thead>
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<th>Type 1</th>
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<tbody>
<tr>
<td>Pain that develops after an initial painful event that may or may not have been traumatic</td>
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<tr>
<td>Allodynia, hyperalgesia, or spontaneous pain is present and is not congruent with the distribution of a single peripheral nerve</td>
</tr>
<tr>
<td>History of edema, skin blood flow abnormalities, or sudomotor abnormalities in the painful region</td>
</tr>
<tr>
<td>No other concomitant conditions account for the pain</td>
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<table>
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<tr>
<th>Type 2</th>
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<tbody>
<tr>
<td>Pain that develops after an identifiable, initial painful event or nerve injury</td>
</tr>
<tr>
<td>Allodynia, hyperalgesia, or spontaneous pain is present and is not congruent with the distribution of a single peripheral nerve</td>
</tr>
<tr>
<td>History of edema, skin blood flow abnormalities, or sudomotor abnormalities in the painful region</td>
</tr>
<tr>
<td>No other concomitant conditions account for the pain</td>
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pabilities, and family obligations. As with other chronic medical conditions, depression is a common comorbidity.

**DIAGNOSTIC TESTING**

Although no specific diagnostic test is available for CRPS, several tests can be supportive in making the diagnosis, but the most important role of testing is to help rule out other conditions. Vascular studies to rule out a vascular etiology are indicated when vasomotor signs and symptoms are prominent. Electrodiagnostic studies may be indicated to rule out specific neuropathic conditions, such as peripheral neuropathy, entrapment neuropathies, or nerve injury. Radiographic studies including magnetic resonance imaging are often necessary to rule out bone or soft tissue pathology as the source of pain. Blood tests including erythrocyte sedimentation rate, blood cell count, and rheumatologic testing may be necessary to help rule out infection or a rheumatologic condition. The diagnosis of CRPS can be made only in the absence of any other diagnosis to explain the findings, eg, diabetic peripheral neuropathy or thoracic outlet syndrome.

In addition to the aforementioned tests, some tests can be obtained to assist in the diagnosis of CRPS. These tests attempt to identify abnormal sympathetic activity or abnormal limb blood flow, but as mentioned previously, these phenomena are not always present. Many of these tests can be used to help monitor the response to treatment; however, reduction of pain and preservation of limb function remain the key indices of successful treatment. The most commonly used tests are discussed subsequently.

**Thermography**

An infrared thermometer (accuracy of ±0.1°C) is used to measure several symmetrical points on the affected and
Sweat Testing
Sudomotor dysfunction is common in patients with CRPS and can be evaluated by several tests that measure sweat output. Subjective sweat testing can be performed by applying an indicator-starch powder to the limbs. The indicator changes color when the limb sweats. Quantitative sweat tests have been shown to correlate with clinical signs of CRPS. The resting sweat output and quantitative sudomotor axon reflex test are valuable tests that measure the sweat output of the affected and unaffected limb. As its name implies, the resting sweat output test is performed to determine the sweat output of the limbs in a resting state. The quantitative sudomotor axon reflex test is a provocative test that determines the sweat output in response to an iontophoresis cholinergic challenge, such as acetylcholine or methacholine.

Radiographic Testing
Plain radiographs can show patchy osteoporosis as early as 2 weeks after onset of CRPS. Disuse and immobilization of the extremity may contribute to this finding. As CRPS progresses, bony structures may have a diffuse ground-glass appearance, and cortical erosions may be present. A 3-phase bone scan of the affected extremity with use of technetium Tc 99m-labeled bisphosphonates is a highly sensitive (but relatively nonspecific) test that may detect osseous changes earlier than plain radiographs. Classic findings include increased periarticular uptake throughout the 3 phases (blood pool, blood phase, scan phase); however, in some patients a reverse or mixed pattern is seen. This variability is influenced by the duration of the patient’s symptoms. Bone densitometry will often reflect a lowered bone mineral density and bone mineral content in affected limbs. These indices often improve in patients undergoing treatment and may be used to monitor treatment efficacy.

Electrodiagnostic Testing
Electromyography can be useful in patients with type 2 CRPS, showing changes consistent with nerve injury. An important distinction between type 2 CRPS and a peripheral mononeuropathy is that in type 2 CRPS, the somatosensory symptoms extend beyond the distribution of the affected peripheral nerve.

Sympathetic Blocks
Based on the old nomenclature system (RSD instead of CRPS), the analgesic response to a sympathetic nerve block was considered an essential piece of diagnostic information. In fact, most pain management experts considered a positive response to a sympathetic block (ie, relief of pain and associated symptoms) to be the most important diagnostic tool. Based on the new system (CRPS), sympathetic dysfunction may or may not play a role. Accordingly, a positive response to a sympathetic block is not required to diagnose CRPS. Some patients do not have sympathetic dysfunction, and it is important to identify these patients because of therapeutic implications. A diagnostic sympathetic block should be considered for patients with clinical evidence of vasomotor or sudomotor dysfunction and severe pain. Patients who experience symptomatic improvement after a sympathetic block may need to have sympathetic blocks incorporated into their treatment program to control the sympathetically maintained component of pain.

A pharmacological sympathetic block can be performed with an intravenous infusion of phentolamine; however, this technique has not gained widespread use. The more common and time-tested approach is to perform a local anesthetic sympathetic trunk block. A lumbar paravertebral sympathetic block is performed for lower extremity symptoms, and a cervicothoracic block (often called stellate ganglion block) or upper thoracic sympathetic block is performed for upper extremity symptoms. Of importance, not all diagnostic sympathetic blocks are created equal. To avoid misinterpretation and misdiagnosis, the procedure must be done in a carefully controlled manner. Most importantly, it is vital to obtain evidence of a satisfactory sympathetic block (eg, thermography) and demonstrate the absence of a somatic nerve block. The latter is important because pain relief from an unrecognized somatic nerve block erroneously ascribed to the sympathetic block may lead to inappropriate diagnosis and treatment. The injected local anesthetic may spread from the sympathetic trunks to the adjacent somatic nerves because the sympathetic nerve trunks supplying the upper and lower extremities are anatomically close to the somatic nerves. A placebo effect may be substantial.

TREATMENT
The selection of a specific technique or a combination of techniques depends on the severity of symptoms and the degree of disability. Of importance, successful treatment of CRPS depends on an aggressive and multidisciplinary approach. Since pain and limb dysfunction are the major
clinical problems, physical rehabilitation and pain control are the main treatment objectives. The selection of pain management modalities is guided by the severity of the pain and the presence or absence of sympathetic dysfunction. Comorbidities such as depression, sleep disturbance, anxiety, and generalized physical deconditioning should be treated.

**Physical Therapeutics**

Physical therapy is the cornerstone and first-line treatment for CRPS. Physical therapy is one of the few interventions that have been shown in controlled studies to be effective. The ultimate goal of physical therapy is to improve function of the patient’s affected extremity. This goal is accomplished by proceeding in an orderly and logical sequence. While adequate analgesia is provided, initial treatment consists of gentle desensitization and may include various combinations of heat, cold, massage, and contrast baths. When the patient can tolerate these measures, gentle flexibility and isometric strengthening exercises are initiated. As the patient improves, treatment consists of more aggressive range-of-motion exercises, stress loading, isotonic strengthening, and general aerobic conditioning. At any or all these stages, pain-control measures are typically needed to enable the patient to participate fully. Normalization of use and vocational/functional rehabilitation comprise the final stages of physical therapy. This stage may include work hardening, vocational rehabilitation or retraining, and workplace modification. Patients may need weeks to several months to progress through this stage.

**Drug Therapy**

Few well-designed medication trials have been performed for CRPS. Many medications have been studied in controlled trials for the treatment of other neuropathic pain conditions, such as diabetic peripheral neuropathy and postherpetic neuralgia. Clinically, the medications that have been found to be useful for treating CRPS include antidepressant agents, gabapentin, corticosteroids, and opioids. Although antidepressant agents and gabapentin are not approved by the Food and Drug Administration for the treatment of neuropathic pain, controlled studies have shown efficacy. Dosage guidelines for the most commonly used medications are given in Table 2.

**Antidepressant Agents.**—At least 3 possible desirable therapeutic effects may result from using an antidepressant. Pain may be reduced, and depressive symptoms may be improved. In addition, several drugs in this class cause sedation, a therapeutic advantage in patients with impaired sleep. The analgesic mechanism is unknown, but it may be related to the known action of norepinephrine and serotonin reuptake inhibition in the central nervous system because both of these neurotransmitters have analgesic effects. Amitriptyline, nortriptyline, and doxepin are the 3 most commonly used drugs in this class. The newer serotonin-specific reuptake inhibitor antidepressants tend to be less effective analgesics and are not used as commonly for pain. The clinician should be familiar with possible adverse effects, including anticholinergic effects (xerostomia and sedation), antiadrenergic effects (postural hypotension), and proarrhythmic cardiac effects.

**Gabapentin.**—Controlled clinical trials have demonstrated that gabapentin is an effective analgesic agent in the treatment of painful diabetic neuropathy and postherpetic neuralgia. It may have some analgesic efficacy in CRPS. Gabapentin is unlikely to be effective as the sole analgesic agent for severe pain, but it may be a useful adjuvant. The pain-relieving mechanism of action of gabapentin has not been determined.

**Corticosteroids.**—Corticosteroids have been reported to be useful in select patients with CRPS. Early in the course of CRPS, the injury response may have a substantial inflammatory component that may respond favorably to a brief course of corticosteroids. The actual mechanism of action of corticosteroids is incompletely understood, but it may involve suppression of ectopic neural discharges in addition to its anti-inflammatory effects. Long-term use of corticosteroids has a questionable risk-benefit ratio, and this strategy is not recommended for patients with CRPS.

**Topical Analgesics.**—Topical capsaicin enhances the release and inhibits the reuptake of substance P and other neuropeptides from terminals of unmyelinated polymodal afferents. Capsaicin has been shown to have an analgesic effect in some neuropathic pain states but has not been studied in CRPS. Patients with CRPS are often unable to tolerate application of topical capsaicin and the subsequent burning sensation.

Lidocaine transdermal patches have been useful for focal CRPS phenomena, such as patch allodynia, but are not

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**Table 2. Medications for Complex Regional Pain Syndrome**

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<thead>
<tr>
<th>Medication</th>
<th>Initial</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>100 qhs</td>
<td>600-1200 tid</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 qhs</td>
<td>75-150 qhs</td>
</tr>
<tr>
<td>Doxepin</td>
<td>10 qhs</td>
<td>75-150 qhs</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10 qhs</td>
<td>75-150 qhs</td>
</tr>
<tr>
<td>Hydrocodone†</td>
<td>5 every 4-6 h prn</td>
<td>5-10 every 4-6 h prn</td>
</tr>
<tr>
<td>Oxycodone SR</td>
<td>10 every 8-12 h</td>
<td>10-80 every 8-12 h prn</td>
</tr>
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*prn = as needed; qhs = at bedtime; SR = sustained release; tid = 3 times daily.
†Available as hydrocodone/acetaminophen, 5 mg/500 mg and 10 mg/500 mg formulation. Total acetaminophen dose should not exceed 4 g per 24-h period.
useful for patients with widespread pain. Use of such patches in patients with CRPS has not yet been studied.

**Opioids.**—Use of opioids for CRPS is controversial because neuropathic pain may respond poorly to opioid therapy. Using an opioid is appropriate when pain is not controlled with more conservative approaches such as heat, ice, or medications such as gabapentin and/or antidepressant agents. Opioids are indicated when pain prevents patient participation in physical therapy and rehabilitation. If an opioid is used, it is important to confirm that it has the intended analgesic effect of allowing patient participation in therapy. If not, then more aggressive interventional approaches may be indicated. Hydrocodone or oxycodone (with or without acetaminophen) is commonly used. Other opioids, including morphine and hydromorphone, are occasionally necessary.

**Other Drugs.**—Anecdotal reports have described successful treatment of CRPS with many other types of drugs; however, such results have not been confirmed in randomized controlled trials. Oral sympatholytic drugs (eg, prazosin), clonidine, ketamine, bisphosphonates, muscle relaxants (eg, cyclobenzaprine), and calcium channel blockers (eg, nifedipine) have been reported to have a therapeutic effect in selected patients. Experience with these agents is too limited to recommend widespread clinical application, but one or more of them may be helpful in individual patients. Similarly, a centrally acting muscle relaxant such as baclofen may be useful in patients with CRPS who have a movement disorder (eg, dystonia, spasticity).

**Regional Anesthesia Techniques**

Patients with moderate to severe pain that does not respond to medication and physical modalities, patients with signs and symptoms of severe sympathetic dysfunction, and patients who experience marked improvement after a diagnostic sympathetic block (sympathetically maintained pain) are candidates for regional anesthetic blocks. The goal is to provide analgesia to facilitate therapy and rehabilitation. The 2 major types of regional techniques are sympathetic nerve blocks and combined somatic/sympathetic nerve blocks. Sympathetic nerve blocks are chosen when the patient has marked improvement after a diagnostic block (as described previously). A properly performed sympathetic block spares sensory and motor function, which allows the patient to participate in therapy. Patients with sympathetically independent pain who do not respond to sympathetic blocks may need a combined somatic/sympathetic block. A series of blocks is considered successful if the patient can participate in physical therapy and progresses in rehabilitation. Continuing the series beyond 2 to 3 weeks is unusual. If severe pain persists beyond that time, long-term pain-relieving options may need to be considered.

**Sympathetic Blocks.**—Despite the lack of large-scale controlled clinical trials, sympathetic nerve blocks have been used for many years to treat RSD and CRPS. A large body of anecdotal literature suggests efficacy. After a successful diagnostic sympathetic block, a series of daily or every other day sympathetic ganglion blocks with use of local anesthetic for 1 to 3 weeks is the preferred approach. Cervical and lumbar sympathetic trunk blocks can be performed as a series of intermittent blocks, or a catheter can be placed next to the sympathetic trunk and local anesthetic boluses performed daily. To maximize advantage of the analgesic effects of the blocks, physical therapy should be initiated immediately after the block. If sympathetic blocks are effective in producing analgesia but duration is limited, neurolysis with either neurolytic injections or radiofrequency-lesioning techniques can be considered.

**Somatic Blocks.**—In a patient with CRPS in whom diagnostic/therapeutic sympathetic ganglion blocks are unsuccessful and the pain is so severe that the patient is unable to participate in the early steps of physical therapy, epidural block or somatic conduction block of the brachial or lumbar plexus can be performed with use of an indwelling catheter. Each procedure coincidentally blocks the sympathetic nerves. Like sympathetic blocks, these blocks can be performed as a series of daily or every other day blocks, or a catheter can be placed for frequent local anesthetic bolusing. This approach can facilitate physical therapy and may reduce the pain to a level that can be controlled with oral analgesics. Special care must be taken during physical therapy because patients may have musculotendinous contractures that may accidentally be injured while they are anesthetized under regional anesthesia. Historically, intravenous regional nerve blocks have been used for treatment of CRPS, but they have not been shown to be helpful and are not used in clinical practice.

**Neuromodulation**

Neuromodulation is manipulation or modulation of central pain pathways by delivery of an electrical current or chemical application to the central neural axis. Clinical experience and recent controlled trials of spinal analgesia and spinal cord stimulation techniques in the treatment of CRPS are promising. These techniques are invasive and should be undertaken only after more conservative measures have failed.

**Spinal Cord Stimulation.**—The mechanism of action of spinal cord stimulation is poorly understood. In addition to modulating pain pathways, there appears to be a sympatholytic effect. In carefully selected patients with CRPS, epidural spinal cord stimulation can reduce pain and improve health-related quality of life.

**Intrathecal Analgesia.**—If reasonable analgesia with oral or transdermal opioid preparations cannot be achieved...
Figure 1. Algorithm for the treatment of complex regional pain syndrome. TCA = tricyclic antidepressant.
because of either lack of efficacy or intolerable adverse effects, intrathecal delivery of opioids or baclofen may be indicated. For a subset of patients with CRPS who have dystonic features, intrathecal baclofen has been shown to decrease dystonia, improve functioning, and occasionally reduce pain levels. Intraspinally and epidurally administered clonidine has been shown to decrease pain in patients with CRPS.

CONCLUSION
Like most medical conditions, early diagnosis and treatment of CRPS increase the likelihood of a successful outcome. Accordingly, patients with clinical signs and symptoms of CRPS after an injury should be referred as soon as possible to a physician with expertise in evaluating and treating this condition. Mild cases respond to physical therapy and physical modalities. Most patients improve with early treatment. A small percentage of patients develop refractory, chronic pain and require long-term multidisciplinary treatment regimen if these medications do not provide sufficient analgesia to allow patients to participate in physical therapy. Patients with moderate to severe pain and/or sympathetic dysfunction require regional anesthetic blockade to participate in physical therapy. Most patients improve with early treatment. A small percentage of patients develop refractory, chronic pain and require long-term multidisciplinary treatment, including physical therapy, psychological support, and pain-relieving measures. Pain-relieving measures include medications, sympathetic/somatic blockade, spinal cord stimulation, and spinal analgesia. A suggested treatment algorithm is depicted in Figure 1.

REFERENCES

Questions About CRPS

1. Which one of the following is not included in the criteria for the diagnosis of CRPS?
   a. Pain that develops after an initial painful event that may or may not have been traumatic
   b. Distribution of the painful area is limited to the distribution of a single peripheral nerve
   c. History of edema, skin blood flow abnormalities, or sudomotor abnormalities in the painful region
   d. No other concomitant conditions account for the pain
   e. Allodynia, hyperalgesia, or spontaneous pain is present

2. Which one of the following is the cornerstone and first-line treatment of CRPS?
   a. Gabapentin
   b. Tricyclic antidepressants
   c. Opioids
   d. Corticosteroids
   e. Physical therapy

3. Which one of the following statements is false?
   a. The sympathetic nervous system is always involved in the mechanism of pain in CRPS
   b. Sympathetic nerve blockade can be helpful in treating CRPS
   c. Somatic nerve blockade can be helpful in treating CRPS
   d. Chronic painful conditions are often accompanied by depression and anxiety
   e. Physical therapy should always be part of the treatment plan for patients with CRPS

4. Which one of the following is not a useful test in supporting the diagnosis of CRPS?
   a. Quantitative sudomotor axonal reflex test
   b. Resting sweat output
   c. Resting skin temperature
   d. Muscle biopsy
   e. Three-phase bone scan

5. Which one of the following statements is true?
   a. Negative response to a sympathetic block excludes the diagnosis of CRPS
   b. Negative response to a somatic block excludes the diagnosis of CRPS
   c. Absence of findings consistent with sympathetic dysfunction during physical examination excludes the diagnosis of CRPS
   d. Normal findings on electromyography of the affected extremity exclude the diagnosis of CRPS
   e. Properly performed sympathetic block spares sensory and motor function

Correct answers:
1. b, 2. e, 3. a, 4. d, 5. e