

**“Transverse Myelitis” chapter in Current Therapy in Neurologic Disease, Sixth edition, Author-Douglas Kerr MD/PhD  
editors, Johnson, R.T, Griffin, J.W., & McArthur, J.C. Mosby Press, 2001**

### **CLINICAL FEATURES OF TM**

Transverse myelitis (TM) is an acute inflammatory process affecting a focal area of the spinal cord. It is characterized clinically by acutely or subacutely developing symptoms and signs of neurological dysfunction in motor, sensory and autonomic nerves and nerve tracts of the spinal cord. There is often a clearly defined rostral border of sensory dysfunction and a spinal MRI and lumbar puncture often show evidence of acute inflammation. Other known neurologic diseases such as compressive myelopathy, syphilis, malignant neoplasm, or spinal AVM should be excluded before the diagnosis of TM is given. Transverse myelopathy is more broadly defined as any acute non-compressive myelopathy with symptoms suggestive of a clearly defined rostral border. Symptoms may progress rapidly over minutes to hours in some TM patients, or may progress over days to weeks in others. When the maximal level of deficit is reached, approximately 50% of patients have lost all movements of their legs, virtually all patients have some degree of bladder dysfunction, and 80-94% of patients have numbness, paresthesias or band like dysesthesias. Autonomic symptoms consist variably of increased urge to urinate, bowel or bladder incontinence, difficulty or inability to void, a sensation of incomplete evacuation or bowel constipation.

TM is a rare disorder with an incidence of between 1-4 new cases per million people per year and. TM can affect people of all ages (range six month old to 88 years old) with peak incidences between the ages of 10-19 and 30-39 years of age. There is no gender or familial predisposition to TM. Approximately 1/3 of patients recover with little to no sequelae following the initial attack, 1/3 are left with moderate degree of permanent disability, and 1/3 have virtually no recovery and are left severely functionally disabled. Several clinical features such as rapid progression of symptoms, the presence of back pain and the presence of spinal shock may serve as poor prognostic indicators for ultimate recovery. Paraclinical evidence such as absent central conduction on evoked potential testing and the presence of 14-3-3 protein in the CSF during the acute phase also predict poor outcomes.

### **ETIOLOGIES OF TM**

There is no single etiology for TM, but in many cases, the clinical syndrome may be a result of damage to neural tissue by an infectious agent or by the immune system or both. Many cases are likely parainfectious, often following a respiratory infection or GI illness. In many fewer cases has TM been shown to be caused by direct microbial infection of the CNS. 30-60% of patients with TM report a preceding infection within 3-8 weeks, and serologic evidence for acute infections with rubella, measles, infectious mononucleosis, influenza, enteroviruses, mycoplasma or hepatitis A, B and C has been demonstrated. Other pathogens such as herpes viruses (CMV, VZV, HSV1 HSV2, HHV6, EBV), HTLV-1, HIV-1 directly infect the spinal cord and can cause the clinical syndrome of TM. *Borrelia burgdorferi* (Lyme neuroborreliosis) and *Treptonema pallidum* (syphilis) have also been associated with direct CNS infection and TM. TM has been associated with systemic autoimmune diseases such as SLE. Several patients were shown to have a focal spinal vasculitis associated with active SLE symptoms, while other patients were shown to have antiphospholipid antibody or the related antibody to beta-2-glycoprotein I. Both antibodies are associated with a pro-thrombotic state, and microvascular thrombosis may underly the clinical syndrome in these patients. Finally, patients with transverse myelopathy will often be ultimately diagnosed with multiple sclerosis.

Important in the differential diagnosis of transverse myelitis is spinal cord ischemia. Arterial, venous and watershed infarcts have been described in patients initially diagnosed with transverse myelitis. Spinal cord infarcts due to arterial occlusion are most common in the anterior spinal artery territory, causing damage to the corticospinal tract, descending micturition/defecation fiber tracts, and the spinothalamic tract with sparing of posterior column function. In the rostrocaudal axis, most arterial infarcts occur in the T4-T10 region due to the limited collateral blood supply in this watershed area. Venous infarction also may occur with progressive neurologic deficits, often with hemorrhagic transformation reflective of persistent venous hypertension. Further, dural AV fistulas cause a stuttering or intermittently progressive myelopathy usually in men between the ages of 40 and 70. This is a diagnosis that should be considered in any patient with recurrent myelopathy since surgical or endovascular embolization therapy may restore neurologic function in some individuals.

### **EVALUATION OF PATIENTS WITH ACUTE TM**

Any patient suspected of having acute spinal cord dysfunction warrants emergent evaluation. Since relatively few patients have the full triad of motor, sensory and autonomic dysfunction at the outset, physicians must have a low threshold for recommending further evaluation. Unfortunately, back pain with a radicular

quality is a common and non-specific early symptom of many patients with TM. However, a patient's complaints of difficulty urinating or new onset incontinence and a transverse sensory complaint (band like pressure, pain or numbness) should prompt the physician to recommend urgent further evaluation. Similarly, bilateral acute progressive leg weakness with any of the above symptoms should prompt rapid evaluation. Many patients, presenting with a rapidly progressive paraparesis, are incorrectly diagnosed with Guillain-Barre Syndrome (GBS). However, in contrast to GBS, TM does not present with cranial nerve palsies, and GBS rarely presents with bladder dysfunction and a band like sensory complaint.

Initial evaluation of a patient with an evolving myelopathy should determine whether a structural cause (e.g. herniated disk, pathologic vertebral fracture, tumor metastasis or spondylolisthesis) can be identified (see acute TM algorithm). Ideally an MRI with gadolinium contrast should be obtained within several hours of presentation. If, however, one cannot be obtained in a short time period, CT-myelography or CT of the spine is a reasonable alternative. These latter two studies have the distinct disadvantage of being unable to assess intramedullary pathology, and all patients diagnosed with TM should have an MRI as soon as possible in the acute phase. If there is a delay in obtaining any imaging study and a patient clinically has a rapidly evolving myelopathy, then methylprednisolone should be empirically administered as follows: <3 hours from symptom onset- 30 mg/kg bolus over one hour followed by 5.4 mg/kg/hour for 23 additional hours; between 3-8 hours from symptom onset- 30 mg/kg bolus followed by 5.4 mg/kg/hour for an additional 47 hours. If a structural cause is identified for the myelopathy, urgent neurosurgical evaluation is mandatory.

If no structural cause is identified for the patient with an acutely or subacutely evolving transverse myelopathy, then treatment is highly dependent on the potential cause. A lumbar puncture should be performed and CSF should be evaluated for routine studies as well as oligoclonal bands, IgG index, viral PCRs, lyme and mycoplasma antibodies, and VDRL. Though this list of studies is not comprehensive, it does identify potentially treatable causes of acute transverse myelopathy. Additional serologic studies may be warranted depending on the clinical scenario. While awaiting the return of serologic and PCR studies, we will often initiate treatment with acyclovir empirically (10 m/kg IV TID for 14-21 days), especially if there is a history of burning, radicular pain or zoster radiculitis preceding the myelitis. If the patient has clinical or radiologic evidence for mycoplasma pneumonia, treatment of the TM should include doxycycline (100 mg PO BID) or azithromycin (500 mg times one, then 250 mg PO qD). Similarly, in the appropriate clinical setting, one needs to consider adding IV ceftriaxone empirically for the diagnosis of neuroborreliosis (Lyme). Immunosuppressed patients with a history of CMV retinopathy or polyradiculopathy should receive gancyclovir (5 mg/kg IV q12). Consideration of a microbiologic etiology for the TM should not dissuade aggressive use of intravenous corticosteroids.

The administration of high dose intravenous steroids is often given once the diagnosis of TM is made, and several small studies have suggested that it improves time to independent ambulation and ultimate motor recovery. Many physicians initiate treatment with methylprednisolone 1000mg IV qD for 5 days, and this regimen should be started in most patients as soon as the diagnosis of TM is considered. Weinschenker and colleagues have shown that a subset of steroid-refractory patients with idiopathic inflammatory demyelinating disorders respond to plasmapheresis. Therefore, at our institution, patients with acute TM are given a five-day course of IV solumedrol followed by plasmapheresis at 1.1 plasma volumes QOD for two weeks. It is unclear presently when to initiate plasmapheresis, but we wait for one week following the completion of the steroids to initiate plasmapheresis.

In TM patients with known or suspected connective tissue disorder such as SLE, investigation should attempt to elicit evidence for a systemic vasculitis, or alternatively, evidence for a pro-thrombotic predisposition on the basis of anti-phospholipid antibodies. Vasculitic etiology may be suspected with lowered complement levels, high ANA titer, hematuria, high ESR or other systemic manifestations of active SLE. Such patients should receive high dose IV corticosteroids and consideration for pulse IV cyclophosphamide (500-1000 mg/m<sup>2</sup>). Subsequent pulses of cyclophosphamide should be given monthly at a dose designed to give a nadir WBC count of 3,000-4,000/mm<sup>3</sup>. SLE patients with antiphospholipid antibodies often report previous arterial or venous thrombotic events, fetal loss, or exhibit livedo reticularis. These patients will often require intensive anticoagulation to prevent recurrent TM and potentially as acute therapy.

## **CHRONIC TREATMENT OF TM PATIENTS**

Since TM is usually a monophasic disorder, treatment of patients following the acute injury focuses on symptom management. Many of these management strategies are similar to those taken with patients with spinal cord injury and will not be reviewed in detail here (see Chapter x, and Chronic TM algorithm next page). Several general guiding principles should be observed in management of patients with TM. If it is at all possible for a patient to stand or walk, this should be done at least daily. Assumption of the upright posture is critical for maintenance of bone and muscle architecture as well as circulatory system reactivity. It also diminishes the incidence of urinary tract infections and deep venous thromboses. Patients may require a standing frame or special orthotic braces, or may require aquatic therapy (see below) in order to do this. TM patients must also be

screened for depression since this is quite common and often leads to decreased compliance with physical therapy regimens and adversely affects ultimate outcome. Sexual dysfunction is a common problem in TM patients, and males with erectile dysfunction often report improved sexual function with sildenafil (50 mg 1 hr before sexual activity, if no response may increase to 100 mg before sexual activity). Patients must be screened for osteoporosis even if young since reduced or absent weightbearing results in accelerated osteoclast-mediated bone resorption. Bone densitometry assessment followed by treatment (Ca<sup>++</sup> 1000 mg/d with Vitamin D 400 I.U./d, and consideration of bisphosphonate treatment) diminishes the likelihood of subsequent pathologic fracture and deterioration in function.

Patients are often left with bladder dysfunction that evolves over time from an atonic bladder initially to one that is spastic with episodes of urinary incontinence. This change is caused by the development of detrusor hyperactivity following damage to descending micturition fibers. Patients with sacral TM (involvement of the conus medullaris) may be left with a permanently acontractile bladder if the lower motor neurons to the bladder are damaged. Renal ultrasound should be obtained within the first three months to evaluate for upper tract damage, and urodynamics testing should be obtained sometime within the first six months following TM to evaluate for high pressure storage and voiding as well as DESD (detrusor-external sphincter dyssynergia). These conditions can predispose to chronic damage both to the upper and lower urinary tracts and are often clinically silent. Further this evaluation will assist the clinician in determining pharmacological treatment to maximize urinary function. The goal of effective management of bladder dysfunction is low storage pressure (<10-15 cm H<sub>2</sub>O), low voiding pressures (<40-60 cm H<sub>2</sub>O in males and <20-30 cm H<sub>2</sub>O in females), and reduction in residual volumes (<50-100 cc). Simple detrusor hyperactivity may be treated by anti-cholinergic medicines such as oxybutinin extended release (5-10 mg qD or BID), hyoscyamine (0.15-0.3 mg PO QID), tolterodine (1-2 mg BID) or propantheline (15 mg PO q4-6), while DESD warrants urological consultation and often combinatorial therapies. Sacral nerve stimulation is a promising new therapy that can allow patients to have reduced or eliminated need for intermittent catheterization.

Patients are often left with permanent weakness following TM. Standard rehabilitative strategies often result in functionally relevant improvement and should be aggressively employed. Aquatic rehabilitation is particularly beneficial in patients with TM for improvement of cardiovascular fitness, reduction in spasticity, resumption of the upright posture, and maintenance of a sense of independence. Some patients report significant improvement in terms of strength and bladder dysfunction with the use of fampridine (4-AP). This drug is a potassium-channel blocker that inhibits the repolarizing current in neurons. It, therefore, enhances conduction of damaged nerves. It should be administered with caution due to potential side effects that include paresthesias, dizziness, agitation, increased blood pressure, insomnia and headache. Fampridine should be started at 10 mg qD and titrated up to a total daily dose of 0.5-0.7 mg/kg/d. Doses higher than 0.8 mg/kg/d have been shown to cause seizures in several patients and should be avoided.

Pain or dysesthesias are the most debilitating long-term sequelae in approximately 40 % of TM patients. Symptoms are often managed by treatment with gabapentin (up to 4800 mg/day divided TID or QID), carbamazepine extended release (up to 1200 mg/d divided BID), nortriptyline (up to 100 mg/d given qHS), or tramadol (up to 400 mg/d divided TID or QID). Opioids are usually no more effective than the above medicines and should be avoided if at all possible secondary to constipation and urinary retention side effects. Intrathecal opioids may be given through an implantable pump and offer significant relief with fewer side effects in selected individuals. TENS units may be applied to a local area of dysesthesias with significant relief of discomfort.

Constipation is a continuing problem in some TM patients often requiring a combination of chronic digital stimulation/disimpaction and laxatives. The goal of bowel management should be the regular evacuation of semiformal feces without the need for chronic straining or pushing. Many patients respond to a regimen of dulcolax (two PO qnoon) and senekot (two PO qnoon). Additionally, the intermittent use of bisacodyl in a water base (The Magic Bullet) is highly effective in the majority of patients.

Spasticity affects virtually all patients with TM and often limits the extent of recovery. Patients may report stiffness, tightness or painful spasms often in the buttocks and legs. The spasticity may limit ambulation, especially on uneven terrain and following stimuli that create postural destabilization. Baclofen (starting at 10 mg qd, titrating up to 100-120 mg/d) is often utilized as first line therapy and is effective in approximately 60% of individuals. Fatigue and the development of weakness are potential side effects. Tizanidine (begin at 2 mg/d titrate up to 24-32 mg/d in three divided doses) is a medication that presynaptically inhibits motor neurons in the spinal cord, and is theoretically more specific for interneurons than is baclofen. It, therefore, may be less likely to cause weakness, but still is limited by fatigue side effects. Diazepam (begin at 5 mg, titrate up to 30-40 mg in three divided doses) may be effective in patients with spasticity not modulated by either tizanidine or baclofen. For patients with functionally limiting spasticity not treated effectively by oral medicines, intrathecal delivery of baclofen is a potentially effective alternative. Following a diagnostic trial of baclofen delivery through a lumbar puncture needle (50 mcg, then if no response 75 mcg or 100 mcg), a subcutaneous pump is implanted which delivers baclofen to the lumbar CSF space. The delivery rate of the pump can be modulated externally, and the

pump has to be refilled percutaneously 3-5 times/year. Potential side effects include pump infection and weakness, but fatigue and worsened constipation usually are not seen.

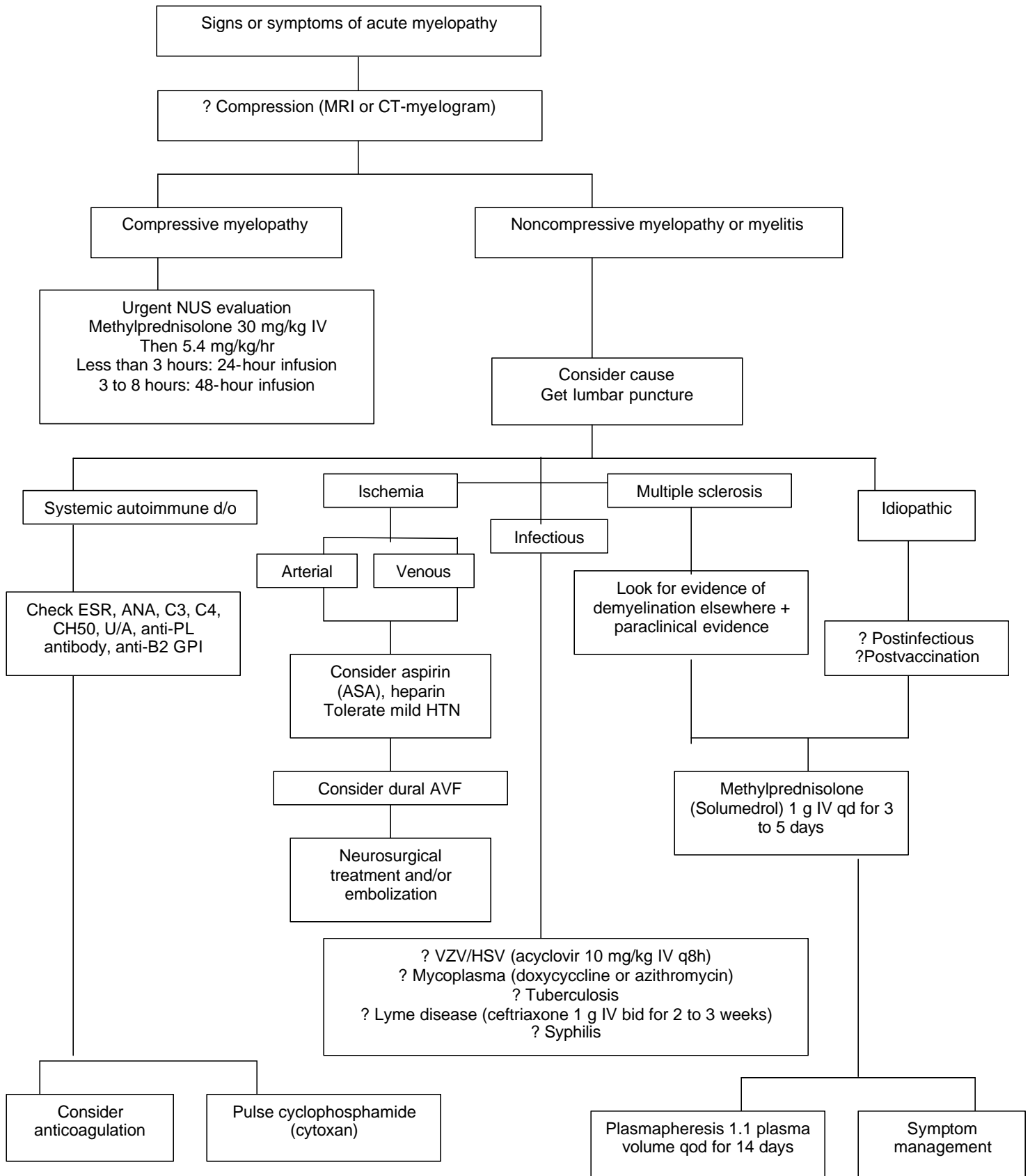
### **Patient Resources**

Transverse Myelitis Association

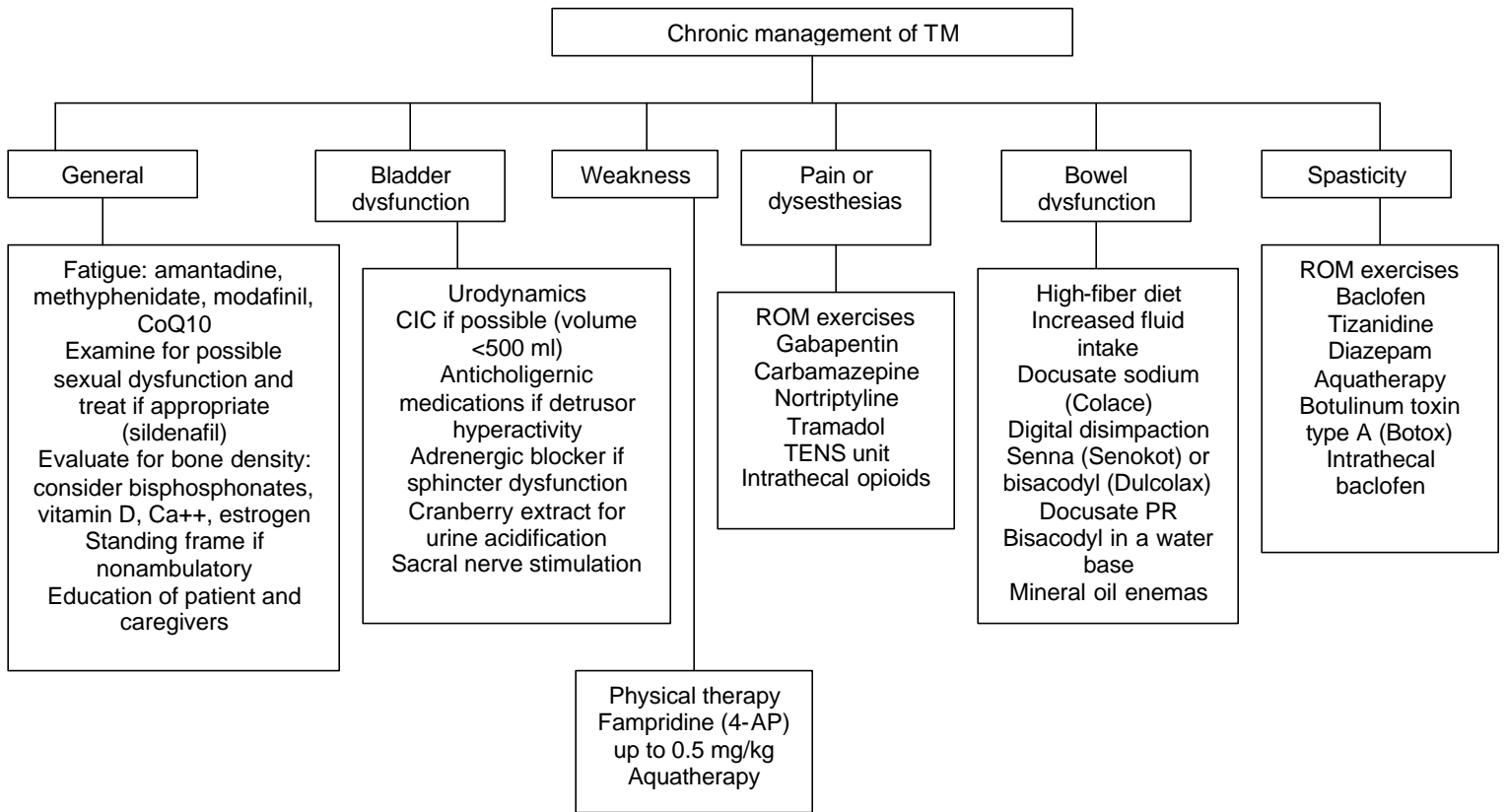
<http://www.myelitis.org>

Johns Hopkins Transverse Myelopathy Center

<http://www.med.jhu.edu/jhtmc>



**Figure 1:** Evaluation of patient for acute myelopathy. ANA, Antinuclear antibody; AVF, arteriovenous fistula; ESR, erythrocyte sedimentation rate; GPI, glycoprotein I; HTN, hypertension; NUS, neurosurgical; U/A, urinalysis; VZV/HSV, varicella-zoster virus or herpes simplex virus.



**Figure 2**

Management of patient with TM. *CIC*, Clean intermittent catheterization; *ROM*, range of motion; *TENS*, transeletrical nerve stimulation