Erythromelalgia

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Mark D.P. Davis, MD*

Thom Rooke, MD

Address

*Department of Dermatology and the Gonda Vascular Center,

Mayo Clinic and Mayo Foundation, 200 First Street, SW,

Rochester, MN 55905, USA.

E-mail: davis.mark2@mayo.edu

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Erythromelalgia is a rare and frequently devastating clinical syndrome. The term erythromelalgia describes the clinical features: erythros (redness), melos (extremity), and algia (pain). It has been suggested that the term should be changed to erythermalgia, to emphasize the thermos (local heat) that is an essential part of the syndrome.

The painful, hot erythema is symmetrical and usually affects the lower extremities, but can also affect the upper extremities. Other body parts (acral) have also been affected similarly. The painful redness and heat is usually intermittent but can be constant. Precipitating factors include exercise and an increase in ambient heat. The associated pain and burning sensation during symptoms can be extremely severe. Patients report major adjustments to their lifestyle in order to avoid precipitating an event. During an episode, patients try to cool their feet in many ways, sometimes resorting to extraordinary measures to alleviate the pain that is experienced, such as putting their feet in ice, and walking in snow.

The pathophysiology of these episodes of erythromelalgia is not understood. In recent years, there has been some light cast on various mechanisms that may be contributing, such as arteriovenous shunting [1] and small fiber neuropathy [2,3]. In inherited erythromelalgia, mutations of voltage-gated sodium channels in sensory nerves have been described [4]. However, the basic pathophysiology has been elusive. Erythromelalgia may be associated with other diseases. Specifically, myeloproliferative disease has been a constant association in studies. Multiple other underlying diseases have been described, but their relationship to the erythromelalgia is unclear.

The natural history of erythromelalgia has been studied in 168 patients by Davis *et al.* [5••]. After a mean follow-up of 8.7 years (range, 1.3 to 20 years), 30 patients (31.9%) reported worsening of symptoms, 25 (26.6%) reported no change in symptoms, 29 (30.9%) reported improvement in symptoms, and 10 (10.6%)

reported complete resolution. Three patients committed suicide because of their symptoms. Kaplan-Meier survival curves revealed a significant decrease in survival compared with that expected in persons of similar age and of the same sex ($P < 0.001$).

The syndrome of erythromelalgia is frequently exacerbated by other factors. An example of this is the treatment employed by afflicted individuals. Patients soak their feet in water and ice, both of which can be associated with freezing or nonfreezing cold injuries of the feet, including "immersion foot" and frostbite. Irritant and allergic contact dermatitis due to substances that have been applied to the affected feet can occur. Other common vascular problems in the lower extremities, such as edema, venous insufficiency, and lymphedema, can be worsened by the erythromelalgia. Patients may have high requirements for pain medications and become addicted to and dependent on narcotic analgesics.

Psychiatric problems, such as depression and obsessive-convulsive behaviors to avoid episodes of erythromelalgia, can occur. The syndrome can be socially disabling, as patients avoid exercise, walking, sports, and sometimes avoid leaving their homes, leading to a sense of disablement, isolation, and loneliness. The syndrome frequently impacts on performance in the workplace (especially with manual jobs or jobs that entail being on one's feet) and at home. A wide spectrum of approaches to the management of patients with erythromelalgia has been used. Because the condition is very rare, almost all of these reports are single case reports or small case series. There has been only one randomized controlled study of a treatment for erythromelalgia [6]—a study of misoprostol versus placebo. Much of the treatment used is based on anecdotal advice. A summary of reported case studies for treatment of erythromelalgia is provided (Table 1) [7–15,16•,17–52]. Anecdotal reports of treatments that are used are also available from surveys of groups of patients with erythromelalgia, one a follow-up survey of 99 patients seen at the Mayo Clinic [5••], the other a follow-up survey of 16 patients who were members of The Erythromelalgia Association [53••]. Both surveys of patients demonstrated that multiple medications are tried by patients with varying efficacy. Because treatments for erythromelalgia are frequently based on anecdotal evidence, patients are frustrated and go from treatment to treatment and doctor to doctor in an effort to find the answer to their problem. In 1938, Smith and Allen [7] wrote, "The treatment of erythermalgia is not uniformly successful"; today, the same statement can be made.

Indications for Hospitalization

Indications for hospitalization include 1) control of severe pain, and 2) management of factors complicating erythromelalgia, such as recalcitrant ulcerations.

Treatment

• An approach to the management of patients with erythromelalgia is outlined in Table 2. It is important to be aware that certain treatments used for erythromelalgia have also been reported to exacerbate erythromelalgia, such as sympathetic blocks, epidurals, sympathectomies, nitroprusside infusions, and calcium antagonists

Diet and Lifestyle

Patient behavior

• *Prevention of episodes:* Patients instinctively seek behaviors that protect them against the development of episodes of erythromelalgia (eg, avoiding exercise or standing for long periods, turning down the heat in the house, sleeping without sheets or blankets on their feet, and a fan directed at the feet).

• *Management of episodes when they occur:* Patients also instinctively seek behaviors that relieve their symptoms during an episode of erythromelalgia. Universally, patients seek situations whereby they can cool their feet during an episode. Some of the more common behaviors that are observed are as follows:

– Going barefoot as much as possible.

– Wearing only open-topped sandals and avoiding wearing socks and shoes.

– Seeking cold surfaces on which to walk (eg, hardwood floors, marble floors).

– Using a fan on the feet during the night or day.

– Putting feet in cold or even iced water during episodes, sometimes for prolonged period

– Using swimming for exercise—the cold water cools the feet. Some patients even take jobs as lifeguards for this reason.

– Some patients use devices used to cool affected extremities (ie, gloves or stocking wraps and cuffs that have ice or iced water in them).

– *Potential complications of these behaviors* include the following:

– Skin damage from constant exposure to cold: freezing or nonfreezing cold injury of the foot, including "immersion foot," frostbite of varying grades, maceration of skin, erosions and ulceration of feet.

– Allergic contact dermatitis due to chemicals and other substances applied to affected skin.

– Exacerbation of any underlying diseases involving legs: venous insufficiency,

arterial insufficiency, and neuropathic changes.

Table 1. Case reports of treatments that have been used in patients with eryt

Therapy used
Aspirin [7–9]
Busulfan (for patients with thrombocytosis) [8]
Capsaicin cream [10]
Serotonin reuptake inhibitors [11]
Tricyclic antidepressants (amitriptyline) [12]
Anticonvulsants (gabapentin) [13]
β Blockers
Propanolol [14]
Labetolol [15]
Prostaglandin E_1 [16•,17,18]
Low molecular weight heparin [19]
Sodium nitroprusside infusions [18,20–22]
Anesthetics
Lidocaine patch [23]
Intravenous lidocaine followed by oral mexiletine [24]
Bupivocaine intermittent [25]
Lumbar epidural infusion with bupivacaine/fentanyl [26]
Cervical epidural infusion with bupivacaine/morphine sulfate and bupivacaine/meperidi
Cervical epidural (morphine and bupivacaine) [28]
Opioid/opioid agonist
Buprenorphine [29]
Intrathecal hydromorphone and clonidine (α2 agonist) [30]
Benzadiazepine (clonazepam) [31]
Antihistamines (cyproheptidine) [32]
Nonsteroidal anti-inflammatory drugs (piroxicam) [33]
Ergot alkaloids
Methysergide maleate [34]
Methysergide and aspirin [35]
Pizotifene [15,36,37]
Systemic corticosteroids
Prednisone [38]
Prednisolone, phenoxybenzamine [39]
Growth hormone [40]
Magnesium [41]
Combination treatment

Table 2. Approach to management of patients with erythromelalgia

1. Educate patient regarding what is known about erythromelalgia, its natural history, an
   treatment options. Advise patients regarding availability of support groups*
2. Teach patients to avoid situations that precipitate erythromelalgia
3. Teach patient techniques that will cool the affected extremities (ie, feet) but do not c
4. Control pain
   - Aspirin*
   - Nonsteroidal anti-inflammatory agents
   - Systemic narcotics (oral, intravenous, delivered via pump)
   - Anesthetic agents (local [lidocaine patch], intravenous [lidocaine], oral [mexiletine], epidu
   - Capsaicin (topical)
   - Drugs acting on the nervous system†
     - Serotonin reuptake inhibitors
     - Tricyclic antidepressants
     - Anticonvulsants
     - Benzodiazepines
     - Ergot alkaloids
   - Sympathectomy, sympathetic nerve block†
   - Nonmedicinal approaches: biofeedback, hypnosis
5. Control secondary factors (leg edema, immersion foot, maceration, derrmatitis, addicti
   psychiatric and psychologic complications)
6. Correct underlying disease (eg, myeloproliferative diseases)
7. Consider disease-modifying drugs and procedures
   - Aspirin
   - Drugs acting on the nervous system
     - Serotonin reuptake inhibitors (venlafaxine, sertraline)
     - Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline)
     - Anticonvulsants (gabapentin)
     - Benzodiazepines
     - Ergot alkaloids
   - Drugs acting on the vascular system
     - Calcium antagonists (diltiazem, others)
     - High-dose oral magnesium
     - Sodium nitroprusside infusions
     - Prostaglandin E_1 infusions
   - Antihistamines
   - Surgical procedures—sympathectomy, sympathetic nerve block†

*Example of support group is The Erythromelalgia Association; E-mail: erythro@ida.net; URL http://

Advice to give to patients in terms of lifestyle changes

• Avoid situations that lead to erythromelalgia episodes.

• During episodes, it is appropriate to try cooling the involved extremities. However, moderation is necessary.

• Avoid the use of iced water; use cool water.

• Avoid prolonged soaking of feet in water. Do not soak feet for more than 5 minutes at a time and do not soak more than three times a day.

Pharmacologic Treatment

• The aims of pharmacologic therapy are to eliminate the occurrence of the erythromelalgia. If this is not possible, the aim of management is to minimize and relieve the pain during episodes, and to minimize the disruption of the normal activities of daily living. The range of drugs used for this disorder is huge and ranges from vasoactive drugs to drugs acting on the nervous system. No treatment is consistently effective in all patients, and the varied response of patients to different drugs suggests that erythromelalgia may be the end point of a variety of processes.

• In cases of erythromelalgia secondary to myeloproliferative disease, erythromelalgia often responds to aspirin or to management of the underlying myeloproliferative disease. Initially, a trial of aspirin is appropriate because this drug is safe and there have been reports of complete resolution of erythromelalgia with initiation of this drug.

• Topical interventions, such as judicious use of fans, cooling of the affected extremities, and use of topical anesthetic medications such as a lidocaine patch or other topical anesthetics, may control erythromelalgia completely or in part: this should be a part of any management regimen.

• In general, many vasoactive drugs (_ blockers, calcium antagonists) are surprisingly ineffective in this disorder, although there are case reports of patients responding to these drugs. Calcium antagonists may also exacerbate the erythromelalgia. Magnesium taken orally has been reported to be beneficial. Potent vasodilators such as sodium nitroprusside have been reported to be effective, particularly in children.

• Prostaglandin inhibitors, including the potent vasodilator intravenous prostaglandin E1 and the orally administered prostaglandin E1 analogue misoprostol, have been demonstrated to be effective. A study by Mork *et al.* [6] is the only double-blind, crossover, placebo-compared study of a drug in erythromelalgia. This study demonstrated that misoprostol is clinically superior to placebo in patients with erythromelalgia.

• In general, drugs used for neuropathy can be very helpful in controlling erythromelalgia: anticonvulsants, tricyclic antidepressants, and serotonin reuptake inhibitors have all been reported to be helpful. Anesthetic agents (eg, lidocaine, bupivacaine) may be used locally, intravenously, orally, epidurally, or intrathecally. Topical lidocaine patches over the area of pain may be used alone or in combination with other treatments [23]. Systemically, intravenous lidocaine and the oral analogue mexiletine may be effective in severe cases. Intravenous, then intramuscular, ketamine in low dose has been described to be helpful in controlling pain in one patient [54]. Topical ketamine (0.5%) combined with amitriptyline (1%) in PLO (pluronic lecithin organogel) gel was helpful in controlling the pain of erythromelalgia in a series [55].

• Immunosuppression (eg, cyclosporine) has been reported in individual reports to be helpful [56]. Case reports detail biofeedback, cognitive-behavioral methods, and hypnosis as also being beneficial [57].

Aspirin

Standard dosage: 325 to 650 mg/d.

Contraindications: Hypersensitivity to salicylates, bleeding disorders

Main side effects: Ulcers, bleeding, hypoglycemia.

Special points: Should be tried as first-line treatment. Most effective in the circumstance of underlying myeloproliferative disease. The response to aspirin is idiosyncratic. Aspirin can be extremely effective in some patients with erythromelalgia, but ineffective for others. Patients with essential thrombocytosis or other forms of underlying myeloproliferative disease seem to have the best response to this drug [58]. In the surveys performed [5••,53••], most patients reported that this treatment was either not effective or minimally effective. Davis *et al.* [5••] reported that more than 50% of 57 patients said aspirin was not helpful at all for their erythromelalgia. Cohen [53••] reported that only one of 16 patients said it was of benefit. In view of the safety of this drug and its effectiveness in some patients, aspirin is considered first-line therapy.

Cost/cost-effectiveness: Cheap, and in those patients it works for, very cost-effective.

Lidocaine and mexiletine

Lidocaine: blocks sodium channels; mechanism of analgesic effect may be peripheral, central, or both.
Mexiletine: class 1B antiarrhythmic drug; also blocks sodium channels.

Standard dosage: Lidocaine patch (5%): apply for 12 h/d, at the part of the day when symptoms are worst. Intravenous infusion: 1 to 4 mg/min; should be administered by a physician familiar with administration of intravenous lidocaine. The regimen varies: in one report [59] lidocaine, 200 mg, in adults (100 mg in children) was infused over 4 hours in a single intravenous infusion, and mexiletine, 200 mg, three times daily was initiated on the second day. Epidural: should be administered by an anesthesiologist familiar with the use of lidocaine. Dosage adjustments are necessary in liver disease.

Contraindications: Hypersensitivity to lidocaine/amide-type anesthetics. Pregnancy category B.

Main side effects: Seizures, drowsiness, tremors, hypotension.

Special points: Lidocaine patches may be helpful alone or may decrease requirement for other medications. Topical lidocaine patches over the area of pain may be used alone or in combination with other treatments [23]. Kuhnert *et al.* [24] reported a 90% reduction in erythromelalgia and associated pain with lidocaine intravenous infusion followed by oral mexiletine; on follow-up the remission had lasted approximately 2 years. Nathan *et al.* [60] reported that lidocaine with transition to mexiletine was very effective in reducing pain and severity of pain episodes in an 11-year-old boy with primary erythromelalgia. Jang *et al*. [61] reported a case of primary erythromelalgia improved by mexiletine. Legroux-Crespel *et al.* [59] reported four patients of a family with familial erythromelalgia all responding to lidocaine with transition to mexiletine: the beneficial effect started within 3 days of initiation of the regimen and lasted for a year in three of the four patients, and 2 years in the remaining patient.

Cost/cost-effectiveness: Lidocaine patch: Expensive but cost-effective when the improvement of quality of life is taken into account and also the low incidence of side effects. Intravenous lidocaine: Necessitates inpatient care and is expensive; there is only one report of it being effective.

Bupivacaine hydrochloride

Standard dosage: Reported uses have been mainly epidural. Should be administered by an anesthesiologist familiar with the use of bupivacaine.

Contraindications :Regional intravenous anesthesia, obstetrical paracervical block anesthesia, shock or myasthenia gravis, hypersensitivity to bupivacaine products, obstetrical anesthesia (0.75% concentration only), sulfite allergy (epinephrine-containing solutions only). Pregnancy category C.

Main side effects: Arterial hypotension, ventricular arrhythmias, central nervous system excitation, tinnitus, central nervous system depression, respiratory arrest.

Special points: Requires epidural, which limits long-term use. Rauck *et al.* [27] reported remissions in two adolescent boys receiving epidural infusions of bupivacaine and opioids.

Cost/cost-effectiveness:Cost-effectiveness data are not available.

Capsaicin

Standard dosage: 0.025% or 0.075% capsaicin topical cream, applied as a thin film three to four times a day. Do not use with heating pad or immediately before or after taking a shower or bath.

Contraindications: Hypersensitivity to capsaicin.

Main side effects: Cough with inhalation, local irritation (burning, stinging, erythema).

Special points: Most patients report that capsaicin is not very helpful. Although one patient's symptoms were reported to improve with topical capsaicin in the case report by Muhiddin *et al.* [10], 81% of 16 patients in the survey by Davis *et al.* [5••] reported that capsaicin was not helpful. None of the four patients reported by Cohen [53••] benefited.

Cost/cost-effectiveness: Cost-effectiveness data are not available.

Serotonin reuptake inhibitors: venlafaxine, sertraline

Standard dosage: Venlafaxine: initial dosage is 75 mg/d in two or three divided doses (once a day for extended-release formulation). Maintenance dosage is 75 to 225 mg/d in two to three divided doses (once a day for extended-release formulation). Dosage titration in 75-mg increments, with a minimum of 4-day intervals. Dosage adjustments are required in renal impairment and liver disease. Sertraline: 50 to 200 mg/d. Dosage adjustment is required in patients with liver disease. Duloxetine: 20 mg orally twice daily to 60 mg daily (once or as 30 mg twice daily).

Contraindications: Venlafaxine: hypersensitivity to venlafaxine hydrochloride, recent or concomitant use of monoamine oxidase inhibitor (MAOI). Pregnancy category C. Sertraline: concurrent use or recent use of MAOIs, hypersensitivity to sertraline products, oral concentrate with disulfiram due to alcohol content. Pregnancy category C. Duloxetine hydrochloride: hypersensitivity to any ingredient of product, concomitant use of MAOIs, uncontrolled narrow-angle glaucoma.

Main side effects: Venlafaxine: nausea, anorexia, sedation, dizziness, dry mouth, insomnia. Sertraline intestinal complaints, tremor, headache, insomnia, male sexual dysfunction. Duloxetine: cough; diarrhea; constipation, dizziness; dry mouth; fever; frequent urination; headache; lack or loss of strength; loss of appetite; muscle aches; nausea; sleepiness or unusual drowsiness; sleeplessness; sore throat; stuffy or runny nose; sweating increased; trouble sleeping; unable to sleep; unusual tiredness or weakness; vomiting; weight loss.

Special points: An improvement in symptoms within a week was reported in a pilot study of 10 patients started on venlafaxine 37.5 mg twice daily [62]. Case reports also detail response of individual patients. Cohen [53••] reported that two out of the three patients surveyed had some improvement in their symptoms with venlafaxine and that six of nine patients who tried sertraline has a response. DiCaudo and Kelley [63] reported alleviation of erythromelalgia with venlafaxine. There are case reports of patients responding to duloxetine.

Cost/cost-effectiveness: Cost-effectiveness data are not available.

Fluoxetine

Standard dosage:20 to 80 mg. Dose adjustments are required in patients with liver disease and geriatrics.

Contraindications: Recent or concomitant treatment with MAOIs or thioridazine. Hypersensitivity to fluoxetine. Pregnancy category C.

Main side effects: Anorexia and weight loss, anxiety, sweating, insomnia, asthenia, tremor, headache,gastrointestinal complaints, lupus-like syndrome.

Special points: Wait at least 5 weeks after discontinuing fluoxetine before starting MAOI therapy.

Cost/cost-effectiveness :Cost-effectiveness data are not available.

Gabapentin

Standard dosage 300 mg three times daily. An alternative regimen of 200 mg three times daily was

administered initially for 2 weeks, followed by 400 mg three times daily for the ensuing 3 months. Another alternative is 200 mg three times a day on the first day of treatment; the dose was increased to 400 mg three times a day on the second day. The maximum time between doses should not exceed 12 hours. Dose adjustments are required in renal impairment.

Contraindications Hypersensitivity to gabapentin. Pregnancy category C.

Main side effects Somnolence, dizziness, ataxia, weight gain, nystagmus, tremor, diplopia.

Special points The anticonvulsant gabapentin has been reported to induce a remission in a child [13]. Cohen [53••] reported that gabapentin reduced erythromelalgia symptoms in all 16 patients who used it, but did not lead to remission of disease. In the survey administered by Davis [55], gabapentin was found to be helpful to a varying extent. Gabapentin has been used for the treatment of familial erythromelalgiapain [64]. Do not abruptly discontinue use.

Cost/cost-effectiveness Cost-effectiveness data are not available.

Clonazepam

Standard dosage :Initial dosage is 0.25 mg twice daily, maintenance dosage is 1 to 4 mg/d. Dosage adjustments are required in patients with liver disease and geriatric patients.

Contraindications: Hypersensitivity to clonazepam products, narrow-angle glaucoma, severe liver disease. Pregnancy category C.

Main side effects: Drowsiness, ataxia, hypotonia, respiratory depression, aggravation of seizures, hypersalivation.

Cost/cost-effectiveness: Cost-effectiveness data are not available.

Amitriptyline hydrochloride

Standard dosage: Initial dosage is 75 mg/d orally, divided in up to three daily doses; maintenance dosage is 50 to 150 mg/d orally, divided in up to three daily doses. Dosage adjustments are required in elderly patients and in those with liver impairment.

Contraindications: Concomitant MAOI use, recent myocardial infarction, hypersensitivity to tricyclic antidepressants. Pregnancy category C.

Main side effects: Drowsiness, arrhythmias, seizures, hypotension, anticholinergic effects, central nervous system effects, agranulocytosis, purpura.

Special points: One patient has been reported to respond to the tricyclic antidepressant amitriptyline [12]. Imipramine has also been noted to be effective.

Cost/cost-effectiveness: Cost-effectiveness data are not available.

Nortriptyline

Standard dosage: 60 to 150 mg/d, in up to three divided doses. Dosage adjustments are required in elderly patients and in those with liver disease.

Contraindications: Concomitant use of MAOIs, recovery after a myocardial infarction, hypersensitivity to nortriptyline or tricyclic antidepressants. Pregnancy category D.

Main side effects: Sedation, cardiovascular effects, anticholinergic effects, weight gain, seizures.

Cost/cost-effectiveness : Cost-effectiveness data are not available.

Propranolol

Standard dosage: Propranolol is in the _-blocker drug class. The initial dosage is 40 mg twice a day, titrated to 120 to 240 mg/d in two to three doses. For long-acting formulations, initial dosage is 80 mg/d, titrated to 120 to 160 mg/d.

Contraindications: Hypersensitivity to propranolol, asthma, bradycardia, second- or third-degree heart block, cardiogenic shock, overt cardiac failure. Pregnancy category C.

Main side effects: Bronchospasm, bradycardia, depression, diarrhea.

Special points _ Blockers were tried by 40 of the 99 patients surveyed by Davis *et al.* [5••]; over half said it did not improve their erythromelalgia.

Cost/cost-effectiveness: Cost-effectiveness data are not available.

Calcium antagonists

Standard dosage: Limited data are available for use in erythromelalgia; diltiazem, 1.5 to 3.5 mg/kg/d (divided in three to four doses), has been used. Standard dosage for diltiazem is 60 mg/d initially, followed by 120 to 480 mg/d. Dose adjustments are necessary in patients with liver disease.

Contraindications : Hypersensitivity to calcium channel blockers, symptomatic hypotension (systolic blood pressure of 90 mm Hg or less), atrial fibrillation/flutter (intravenous administration only), heart block, sick sinus syndrome, Wolff-Parkinson-White syndrome, acute myocardial infarction with pulmonary congestion on radiograph, newborns (injection only). Pregnancy category C.

Main side effects: Headache, dizziness, fainting, peripheral edema, gingival hyperplasia, atrioventricular block, bradycardia.

Special points: Calcium antagonists are potent vasodilators that selectively block the movement of calcium ions in the slow channels, leading to decreased smooth muscle contractility. They may also inhibit vascular responses evoked by _2 adrenoceptor activity. Although calcium antagonists have been advocated for the management of patients with erythromelalgia, it is important to remember that they have also been implicated in the causation of erythromelalgia. Reports of patients benefiting from calcium antagonists are sparse, but it seems that this group of drugs is not used infrequently. Cohen [53••] reported that six of 14 patients benefited from the use of diltiazem. Davis *et al.* [5••] reported that the vast majority of the 20 patients who used vasodilator drugs said their symptoms did not improve.

Cost/cost-effectiveness: Generic formulations are available. Prices range from $12 for 100 tablets in a strength of 30 mg, to $86 for 100 tablets in a strength of 120 mg. Benefits are modest and exacerbation of disease has been reported.

Magnesium

Standard dosage Cohen [41] used up to 7 g/d orally. The standard dosage was obtained in various ways; one method was taking intravenous-grade magnesium sulfate diluted in water orally

(up to 24 mL/d of magnesium sulfate 50%, to 1166 mg/d of magnesium); different preparations were used by the other patients who used magnesium.

Contraindications Heart block, severe renal disease, 2 hours preceding childbirth. Pregnancy category B.

Main side effects Flushing, hypotension, muscle weakness.

Special points In a study of the use of magnesium in patients with erythromelalgia, a patient

(the author) reported excellent control of his erythromelalgia. Based on this, he suggested to a group of patients (all members of The Erythromelalgia Association) that they try this therapy. Various doses and forms of magnesium were taken by these patients. Of the 13 patients who reported that they had used magnesium, eight reported improvement (one remission, three major improvements, two

moderate improvements, and two mild improvements), four reported no response and one patient's symptoms worsened [41]. The rationale behind taking the magnesium was that magnesium has some calcium antagonist properties. Intravenous magnesium has been reported to be useful for neuropathic pain [65].

Cost/cost-effectiveness Cost-effectiveness data are not available.

Sodium nitroprusside

Standard dosage Initial 0.3-_g/kg/min intravenous infusion; titrate to 2 to 4 _g/kg/min. Administration

should be by a device that allows precise measurement of the flow rate. In the patient reported by Ozsoylu *et al.* [20], the 9-year-old girl responded to a dose gradually escalated from 1 _g/kg/min to 3 _g/kg/min and then to 5 _g/kg/min.

Contraindications Hypersensitivity to nitroprusside, anemia, head trauma, encephalopathy, symptomatic hypotension, compensatory hypertension (aortic coarctation or atriovenous

shunting), optic atrophy, tobacco amblyopia.

Main side effects Adverse effects from nitroprusside include methemoglobinemia, hypotension,

headache, dizziness, drowsiness, confusion, intracranial hypertension, hypothyroidism, metabolic acidosis, cyanide toxicity, nausea, vomiting, abdominal cramps, abdominal pain, and nephrotoxicity.

Special points Sodium nitroprusside was reported to be useful in a few case reports of pediatric

patients with erythromelalgia [18,20,21]. One adult patient who was surveyed said that his symptoms worsened [53••].

Cost/cost-effectiveness Cost-effectiveness data are not available.

Prostaglandin E1 and iloprost

Prostaglandin E1 is a potent vasodilator, involving arterioles, precapillary sphincters, and postcapillary venules; in addition, it inhibits platelet aggregation. Iloprost is a synthetic prostacyclin analogue.

Standard dosage Prostaglandin E1 was given as continuous infusion for 3 days, starting at a dosage of 6, then 10, and finally 12 ng/kg/min via a peripheral vein by Kvernebo *et al.* [16•,18].

Contraindications Priapism, neonatal respiratory distress syndrome, hypersensitivity to alprostadil,

sickle cell anemia, myeloma, leukemia, women, Peyronie's disease.

Main side effects The most common side effects include flushing, nausea, abdominal cramps,

tachycardia, hypotension, general malaise, and edema. Penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported.

Special points Kvernebo *et al.* [16•,18] reported improvement with infusion of prostaglandin E1 in eight of nine patients (with remission varying from 3 months to 2 years). The improvement occurred after some hours in some patients, but not until day 3 to 4 in others. Littleford *et al.* [17] reported response in one patient. In a double-blind randomized pilot study of the synthetic prostacyclin analogue iloprost, a significant reduction in symptoms in the patients receiving iloprost ($n = 8$) compared with placebo ($n = 4$) was reported [66]. Comment: Both drugs need to be administered intravenously and patients need to be closely monitored. In the United States, it may be difficult to obtain these drugs.

Cost/cost-effectiveness Cost-effectiveness data are not available.

Misoprostol

Standard dosage Misoprostol is a synthetic prostaglandin E1 analogue. Standard dosage is 100 to 200 _g four times a day or 400 _g twice a day. A pediatric dosage is not established.

Contraindications Hypersensitivity to misoprostol or prostaglandins. Pregnancy category X.

Main side effects Diarrhea, abdominal pain.

Special points Mork and Kvernebo [67••] found improvement in 17 of 22 patients with erythromelalgia, including one remission, after 3 months of therapy with misoprostol, compared with improvement in five of 22 patients who received placebo. In a subsequent double-blind, crossover, placebo-compared study of misoprostol (0.4 to 0.8 mg/d for 6 weeks), all clinical outcome measures were significantly better after treatment with misoprostol compared with placebo treatment and after a 3-month follow-up without treatment [6].

Cost/cost-effectiveness Cost-effectiveness data are not available.

Diphenhydramine

Standard dosage 25 to 50 mg orally every 4 to 8 hours.

Contraindications Hypersensitivity to diphenhydramine, MAOI therapy, lactation, newborns and premature infants, narrow-angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, asthma. Pregnancy category B.

Main side effects Dyskinesias, anaphylaxis, sedation.

Special points Although antihistamines have been reported to be helpful for some patients [53••], Davis *et al.* [5••] reported that less than 25% of the 28 patients surveyed who were prescribed antihistamines for their erythromelalgia said that they were helpful.

Cost/cost-effectiveness Cost-effectiveness data are not available.

• Two patients experienced relief of pain following nerve block [68].

Stereotactic surgery of erythromelalgia was reported in the former Union of Soviet Socialist Republics as being helpful in one patient [51]. Destruction
of the inlet areas for the posterior spinal nerve root has also been reported to be beneficial [69]. One patient has been reported to have some relief of

pain with dorsal column stimulation [50]. Thalamic stimulation (bilateral

electrical stimulation of the ventral posterolateral thalamic nucleus) was

successful in a case of primary erythromelalgia [70].

Sympathectomy

Standard procedure Pre- or postganglionic sympathectomy of the cervicothoracic or lumbosacral area.

There are several approaches that can be used; endoscopy is also possible for

cervicothoracic sympathectomies.

Contraindications None.

Complications Pleural effusion and pneumothorax with cervicothroacic procedures, neuralgia,

wound hematomas, and sepsis with all procedures. Horner's syndrome may occur,

especially if the stellate ganglion is removed. Dry skin occurs in the denervated

area. Increased sweating may occur on the trunk.

Special points Mixed results have been reported with sympathectomy [44,45]. Most of the reports demonstrate improvements in symptoms. One patient was made worse by a unilateral sympathectomy.

Cost/cost-effectiveness Surgical and hospital costs are large. Cervicothoracic sympathectomy is not costeffective, but lumbar and digital sympathectomies may be of benefit to some patients.

• A support group is important and helpful to many patients. An excellent source of information for patients is The Erythromelalgia Association (http://www.erythromelalgia.org/), an international, all-volunteer organization serving patients, families, and friends. The Erythromelalgia Association raises funds for research on erythromelalgia, offers education and support to all those affected, and strives to increase awareness about erythromelalgia.

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