Myasthenia Gravis

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Abstract

The basic abnormality in myasthenia gravis (MG) is a reduction in acetylcholine receptors (AChRs) at neuromuscular junctions due to the effects of autoantibodies that are directed against the AChRs in most patients, or against neighboring proteins involved in the clustering of AChRs (MuSK, LRP-4, or agrin). Clinically, MG is characterized by muscle weakness and fatigue, often in typical patterns. The diagnosis may be missed early, and depends on the recognition of clinical manifestations, the measurement of autoantibodies, and/or electrophysiological features. The treatment of MG involves the enhancement of neuromuscular transmission by anticholinesterase drugs (pyridostigmine), and by immunotherapy. Therapy should be designed to improve the clinical features quickly, and keep the symptoms in abeyance over the long term. Rapid improvement can be achieved when necessary by the administration of intravenous immunoglobulin or plasma exchange. Intermediate rates of improvement over months involve the use of adrenal corticosteroids, the calcineurin inhibitors cyclosporine or tacrolimus, and in some patients, the B-cell inhibitor rituximab. For long-term treatment, mycophenolate and azathioprine are the most effective agents. A thymectomy may also have long-term beneficial effects. The majority of MG patients can live normal lives, but most patients require lifelong treatment. The physician's skill in managing the immunotherapeutic agents and avoiding adverse side effects is of paramount importance in the treatment of MG.

Keywords
- myasthenia gravis
- acetylcholine receptors
- autoimmunity
- antibodies
- immunotherapy

Myasthenia gravis (MG) is the best understood human autoimmune disease, and is presently the most treatable neuromuscular disease. Yet it often goes undiagnosed for long periods, and is frequently poorly treated by physicians who do not see many patients with MG. This brief overview will help the clinician to identify and manage MG patients.

Overview

The basic abnormality in MG is a reduction in the acetylcholine receptors (AChRs) at neuromuscular junctions due to the effects of autoantibodies. About 85% of patients with generalized MG have antibodies to AChRs, but only approximately 50% of patients with purely ocular manifestations (ocular MG) have detectable antibodies.[1] Antibodies to another protein at the neuromuscular junction (muscle-specific kinase, or MuSK) are present in approximately 40% of AChR antibody-negative patients with generalized MG.[2] Antibodies to another protein, LRP-4 (low-density lipoprotein receptor-4) are present in a small minority of AChR antibody-negative MG patients, and antibodies to agrin are even rarer.[3] These antibodies are key to making the diagnosis of MG in most patients.

Clinically, MG is manifested by fatigable weakness—weakness that increases with muscle use and tends to improve with rest. The particular muscles that are affected vary in different patients. Commonly, extraocular muscles are affected early, giving rise to diplopia and ptosis. If weakness remains confined to the extraocular muscles for a period of 3 years, it rarely becomes generalized. However, more often the weakness becomes more generalized and any muscle group can be involved, with weakness of proximal limb muscles, dysphagia, respiratory insufficiency, and so on. In questioning a patient with suspected or known MG, I ask about diplopia, ptosis, weakness of arms (fixing hair, dressing, lifting half-gallon

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containers) and legs (walking, going up stairs), speech, voice, chewing, swallowing, and respiration (including orthopnea). Impairment of sensation or autonomic function is not a feature of MG, and the presence of sensory or autonomic abnormalities suggests another diagnosis.

It is critical to make a definite diagnosis of MG before starting treatment because other treatable conditions may resemble MG, and the treatment of MG may involve the prolonged use of drugs with potentially adverse side effects or a surgical thymectomy.[4] The first step is to suspect MG based on the cardinal symptoms restricted to fatigable weakness, especially in a typical distribution. A complete neurologic examination should show weakness and muscle fatigue, without the loss of reflexes or sensation (unless more than one condition is present). A serious pitfall is to treat for MG before making a definitive diagnosis. Such inadequately diagnosed patients are often referred to us because they do not respond to treatment, requiring the discontinuation of medications to determine the appropriate diagnosis and course of therapy.

Diagnostic tests for MG are as follows:

1. AChR antibodies (i.e., antibodies that bind to AChR are diagnostically useful). Although I first defined "blocking" and "modulating" antibodies, they are virtually never positive in patients without binding anti-AChR antibodies. Their scientific value is to help in evaluating the pathogenic roles of AChR antibodies, but they are virtually never helpful in diagnosis.
2. In patients with generalized MG who are negative for AChR antibodies, MuSK antibodies may be present, or less commonly, antibodies to LRP-4 or rarely to agrin. Patients with purely ocular MG very rarely have anti-MuSK antibodies. Anti-AChR and anti-MuSK antibody tests are commercially available.
3. Tests for LPR-4 and agrin antibodies: Antibodies to LRP-4 or agrin can be tested at Georgia Regents University, Neurology Department, 1120 15th St, BP∼4367, Augusta, GA 30912, Attn: Brandy Quarles).
4. Electrodiagnostic tests for MG include repetitive nerve stimulation (which should always be tested in an affected muscle) and single-fiber electromyography. Single-fiber electromyography is a sensitive but not absolutely specific test, and should only be performed by an experienced electromyographer.
5. The edrophonium test is rarely used because of a small but real cardiovascular risk. If needed, it should be done with an anesthesiologist, intensivist, or emergency medicine clinician present to monitor cardiovascular function, and with a syringe containing atropine available. An objective measure of weakness should be noted, then 2 mg of edrophonium given intravenously. If improvement in the weakness occurs, the test is positive and is terminated. If not, then an additional 8 mg are given, and the patient checked for improvement during the next 30 seconds to 5 minutes. If significant bradycardia occurs, atropine should be administered.
6. An additional cost-effective and noninvasive diagnostic tool is the "ice pack test," which entails the application of a packet of ice onto the eyes for approximately 5 minutes. If the ptosis resolves, the test is considered positive.[5]

Myasthenic weakness may involve any skeletal muscle or group of muscles, depending on the individual patient. It is therefore important to document which muscles are involved and the degree of involvement. ►**Fig. 1** is a worksheet designed to document both the patient's subjective awareness of muscle involvement as well as the physician's objective assessment. Quantitative measurements are extremely helpful; we measure vital capacity, timed ability to maintain the arms in forward abduction (all the way to 5 minutes), and hand-held dynamometry.[6] Because most practicing neurologists do not have dynamometers, the Medical Research Council (MRC) Scale is a fair approximation, but if you see enough neuromuscular patients in your practice I recommend using a dynamometer.[6] The "slurp test" in which a patient is timed drinking liquid through a straw is a useful bedside test to monitor swallowing[7] 100 mL of water should be swallowed within less than 10 seconds. Impairment of respiration or swallowing is considered "myasthenic crisis." Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually consists of respiratory failure caused by diaphragmatic and intercostal muscle weakness. Crisis rarely occurs in properly managed patients. Treatment should be carried out in an intensive care unit staffed with teams experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. The most common cause of crisis is intercurrent infection. This should be treated immediately because the mechanical and immunologic defenses of the patient can be assumed to be compromised. The myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy is critical, but antibiotics that can exacerbate MG such as quinolones or aminoglycosides should be avoided. The much less common possibility that deterioration could be due to excessive anticholinesterase medication ("cholinergic crisis") is best excluded by temporarily stopping anticholinesterase drugs. Respiratory assistance should be provided before a respiratory emergency occurs; if possible, noninvasive assistance using bilevel positive airway pressure (BiPAP) is preferable to intubation. Pulmonary physiotherapy is often useful as well. Plasmapheresis or intravenous immunoglobulin (IVIG) is usually helpful in hastening recovery. Although it is easier to arrange for IVIG treatment, most clinicians find that plasmapheresis is more effective, and it is common to have IVIG given for several days, only to have the IgG washed out later by plasmapheresis that is eventually used. Anti-ChE agents should only be given when respiratory assistance is being discontinued, as they do not serve a useful purpose in ventilated patients.

The differential diagnosis of MG involves other conditions that produce weakness, including congenital myasthenic syndromes (usually occurring in childhood), Lambert-Eaton syndrome (usually with hyporeflexia and autonomic symptoms such as impotence and dry mouth), intracranial mass lesions that can give rise to similar ocular manifestations, and mitochondrial disorders (progressive external ophthalmoplegia [PEO]).

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MYASTHENIA GRAVIS WORKSHEET

NAME: _____ DATE: _____
DOB: _____ HISTORY: _____

MEDICATIONS DOSE SIDE EFFECTS

Mestinon_____
Prednisone_____
Imuran_____
CellCept_____
Other_____
Other_____
Other_____

SUBJECTIVE

Diplopia	None	Rare	Occasional	Constant
Ptosis	None	Rare	Occasional	Constant
Arms	Normal	Slightly Limited	Some ADL Impairment	Definitely Limited
Legs	Normal	Walks/Runs Fatigues	Can walk limited Distances	Minimal Walking
Speech	Normal	Dysarthric	Severely Dysarthric	Unintellible
Voice	Normal	Fades	Impaired	Severely Impaired
Chew	Normal	Fatigue on normal Foods	Fatigue on soft foods	N-G tube
Swallow	Normal	Normal Foods	Soft foods only	N-G tube
Respiration	Normal	Dyspnea on unusual Effort	Dyspnea on any Effort	Dyspnea on rest
General	Normal	Good	Fair	Poor

OBJECTIVE

BP: _____ Pulse: _____ Age: ____ HT: ____ WT: _____

Cataracts? Yes / No R ○ L ○

	1	2	3
FEV1			
FVC			

Predicted FVC: _____ %FVC
Diplopia: _____ Ptosis Time: _____
Edema: _____ Face: _____
Arm Abduction: R_____ L_____
Deltoids: R_____ L_____
Biceps: R_____ L_____
Triceps: R_____ L_____
Wrist Ext: R_____ L_____
Grip: R_____ L_____
Illiopsoas: R_____ L_____
Quadriceps: R_____ L_____
Hamstring: R_____ L_____
Tibialis Ant: R_____ L_____

Neck: Flexion _____ Ext: _____
Tongue: _____
Slurp test: _____

NOTES: _____

Fig. 1 Myasthenia gravis clinical worksheet.

Associated Conditions

Every MG patient needs a thorough medical evaluation before beginning treatment. Myasthenic patients have an increased incidence of related conditions, and may also have medical conditions that influence the choice of therapy. Thymic abnormalities occur in 75% of MG patients. Most abnormal thymuses are "hyperplastic": They contain germinal centers (although the thymus may not be grossly enlarged). About 12% of MG patients have thymomas that can be detected by computed tomography (CT) of the thorax. Thymic tissue is normally visible on CT in younger people, but beyond the age of 40, a mediastinal mass in an MG patient is highly suspicious of thymoma. Up to 8% of MG patients have autoimmune thyroid conditions (Hashimoto's thyroiditis or Graves' disease). Importantly, alterations of thyroid status (hypo- or hyper-) can exacerbate the weakness of MG. Graves' disease can mimic features of ocular MG. Other autoimmune disorders occur in association with MG, including rheumatoid arthritis, systemic lupus erythematosus, dermatologic conditions (vitiligo, pemphigus), and hematologic conditions (red blood cell aplasia). In view of the agents used to treat MG, it is important to evaluate the patient's overall medical condition for diabetes, hypertension, renal insufficiency, osteoporosis, and infections such as hepatitis or tuberculosis.

Treatment

The great majority of MG patients can now be treated successfully and restored to fully productive lives. The most useful treatments include anticholinesterase agents, immunosuppressive drugs, thymectomy, and IVIG or plasmapheresis.

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The first decision is to determine the urgency of treatment. Obviously, the severity of involvement will influence the urgency, so that patients with impairment of respiration or swallowing (in "crisis") must be treated promptly and vigorously. Other considerations may include the need to restore single vision (for work purposes, driving, etc.), or the need to produce rapid improvement for patients who come from a distance.

Anticholinesterase (anti-ChE) agents (e.g., pyridostigmine or Mestinon, Valeant Pharmaceuticals) produce quick and at least partial benefit in most MG patients (though they are less helpful in patients with anti-MuSK antibodies). The onset of effect is approximately 20 minutes, and duration of effect is approximately 4 hours. The dose should be adjusted to provide benefit without adverse side effects (mainly gastrointestinal [GI] symptoms such as diarrhea), usually by starting with 30 to 60 mg 3 times per day. Anti-ChE agents may be considered almost like symptomatic treatment because they can help to relieve the symptoms, but do not deal with the underlying autoimmune problem. The improvement often diminishes over time, and few patients derive enough benefit that anti-ChE agents are sufficient alone in the management of their disease. Long-acting ("Timespan") Mestinon should only be used at night if the patient needs help to get through the night or when awakening in the morning. Variable absorption makes long-acting Mestinon a poor choice during the day.

Immunosuppressive agents are the mainstay of treatment. It is important to devise a "time-linked" treatment plan that will work over the short term, intermediate term, and long term. Relatively rapid benefit can be obtained with IVIG, which usually produces improvement within a week or two at the most.[8] In fact, IVIG may be used as a quasidiagnostic test to evaluate whether the patient has MG based on the response. For the intermediate term, glucocorticoids, cyclosporine, or tacrolimus are the drugs of choice.[9] Glucocorticoids are very helpful, but have many potential side effects; we try to maintain the dose at relatively low levels, such as 20 to 40 mg of prednisone per day at the most. Tacrolimus and cyclosporine are metabolized variably by different patients, and the dose must be adjusted by following the "trough" level (which is the serum level at exactly 12 hours after the evening dose). We usually start patients with tacrolimus at a dose of 0.035 mg/kg twice daily, and adjust it up or down as needed. For tacrolimus, the trough level should be 6 to 9 ng/mL. Cyclosporine (Neoral, Novartis Pharmaceuticals) is given at 2 mg/kg twice daily, and adjusted to maintain the trough level at approximately 150 ng/mL Both of these drugs act as calcineurin inhibitors, and inhibit T cells that otherwise provide "help" for antibody-producing B cells. Because they may be nephrotoxic, the patient's renal function (creatinine, blood urea nitrogen [BUN]) must be followed. Although many neurologists hesitate to use these agents, they are really quite simple if the above rules are followed (see ►**Table 1**).

For long-term benefit, we use mycophenolate, typically at a dose of 1 or 1.5 g twice daily. Mycophenolate is often helpful and effective, but may take many months to a year to exert its major effect (because it does not destroy the already existing autoimmune lymphocytes, but rather prevents the synthesis of new ones).[10] Imuran (azathioprine; Prometheus Laboratories) is another drug that works over the long term. It is less expensive than mycophenolate, and similarly effective. It must never be given with allopurinol (a gout treatment). Allopurinol may raise azathioprine's concentration (as they are both metabolized by the same enzyme system).

Patients who are treated with immunosuppressive agents should be followed at intervals (several times a year) by their neurologist (see ►**Fig. 1**). Because immunosuppressive agents may lower resistance to infection, patients should be treated promptly at the early signs of infection. When starting any immunosuppressive agent, blood tests should be performed every 2 weeks until trough levels, blood counts, and metabolic tests are stable; blood tests should be performed for a complete blood count (CBC) and differential, as well as a comprehensive metabolic panel at least 3 to 4 times per year. Attention should be paid to the potential for reactivating tuberculosis (TB) in high-risk individuals, and a skin test or QuantiFERON (Cellestis Inc.) blood test checked before starting immunosuppressants. Because immunosuppressive agents can depress the bone marrow, it is important to follow the CBC. Creatinine should be followed in patients on calcineurin inhibitors (cyclosporine and tacrolimus), which may have nephrotoxic effects, and liver function tests should be watched in patients who receive azathioprine.

Rituximab is an antibody against CD20, a surface component of B lymphocytes (the lymphocytes that are involved in antibody production as well as antigen presentation). Rituximab may be effective treatment for MG, especially in patients with anti-MuSK (rather than AChR) antibodies. AChR antibodies may be produced by the plasma cells (more mature B-type cells), which are not susceptible to rituximab treatment. The dose of rituximab is based on the patient's calculated surface area (easily computed by web-based formulas), and should be 375 mg/m^2 given weekly for four treatments. Patients may benefit within weeks, or may require a second course of four treatments 2 or 3 months later. After the first or second treatment, the circulating CD20 lymphocyte subset should be 0.[11]

Intravenous Immunoglobulin

Intravenous immunoglobulin at a dose of 2 g/kg divided over four or five infusions often produces improvement of MG symptoms within days to 1 to 2 weeks. It should be used for a quick temporary benefit. The mechanism by which it produces benefit is debated, but it does not affect the underlying autoimmune process. All too often physicians resort to repeated IVIG treatments for their patients, which may keep them functioning, but fails to deal with the underlying autoimmune problem. A therapeutic trial of IVIG is sometimes helpful to determine whether a patient with questionable MG shows improvement.

Plasmapheresis

Removal of antibodies by plasmapheresis is reserved for treatment of severe MG, typically in the setting of crisis. The plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are

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Table 1 Time-linked myasthenia gravis treatment plan

Medication	Time to effect	Dose	Side effects	Notes
Short term				
Pyridostigmine	20 min × 4 h	30–60 mg tid	Diarrhea, bradycardia	Caution in bronchial asthma. For night or morning weakness, may use 180 mg "Timespan"
IVIG	Improvement within 2 wk	2 g/kg divided over 4 or 5 infusions	Tachycardia, hyper/hypotension Rare: fluid overload or thrombosis	
Plasmapheresis	Days to 1 wk	5 or 6 total exchanges of 2 to 3 L each, every other day	Hypotension Arrhythmias	
Intermediate term				
Glucocorticoids (prednisone)		20–40 mg/d	Osteoporosis, weight gain, mood disturbances, acne	Check for latent TB prior to starting any immunosuppressants
Cyclosporine (Neoral)		2 mg/kg bid[a]	Nephrotoxic	
Tacrolimus		0.035 mg/kg bid[a]	Nephrotoxic	
Long term*				
Mycophenolate	Months to 1 year	1 or 1.5 g bid	GI upset	Give "Myfortic" 720 mg bid if GI problems with mycophenolate
Azathioprine	Many months		Infections, diarrhea, nausea	Never give with allopurinol- Myelotoxic
Rituximab	May benefit within weeks, or may require a second course of 4 treatments 2 or 3 mo later	375 mg/m^2 weekly for 4 wk	Headache, fever, diarrhea, flushing	Premedicate with methylprednisolone 50–100 mg, Benadryl. Better for anti-MuSK than for anti-AChR Ab MG

Abbreviations: bid, twice daily; GI, gastrointestinal; IVIG, intravenous immunoglobulin; TB, tuberculosis; tid, three times daily.
[a]Dose must be adjusted by following the "trough" level (serum level at exactly 12 h after the evening dose). Please see complete prescribing information prior to administering any of the medications noted in the Table.

returned to the patient. Plasmapheresis produces a relatively rapid reduction in autoantibodies, with clinical improvement in many AChR-antibody positive as well as MuSK-antibody-positive patients. It is useful as a temporary expedient in seriously affected patients, or to improve the patient's condition prior to surgery (e.g., thymectomy). A typical course of plasmapheresis consists of 5 or 6 total exchanges of 2 to 3 L each, every other day. The need for large-bore venous access, usually requiring the surgical insertion of a double-lumen catheter, and the risk of infection related to the indwelling catheter, limit the use of plasmapheresis.

Thymectomy

As noted above, approximately 75% of AChR Ab-positive MG patients have thymic abnormalities, with either germinal center formation ("hyperplasia") in approximately 65%, or thymoma in approximately 11%. Thymic abnormalities are uncommon in patients with MuSK antibody. There are two different indications for surgical thymectomy: (1) For removal of a thymic tumor, or (2) as a treatment for MG. Thymic tumors must be removed because they may spread locally, and involve important structures within the chest, although they rarely metastasize. If the surgical margins are not clear, postoperative radiation is recommended, and chemotherapy may be required. Thymomas may respond to corticosteroid treatment as well. Thymectomy as a treatment for generalized MG is widely advocated, and an international study of its effectiveness will soon be published. Previous studies suggest that about one-third of patients achieve excellent results, one-third improve, and one-third obtain no clinical benefit. The surgical method for thymectomy is a matter of controversy, with some surgeons advocating video-assisted or robotic methods. We agree with those who favor a sternal splitting incision to achieve the most complete removal. The earlier in the course that thymectomy is performed, the more rapidly its beneficial effect is likely to be realized. Thymectomy should never be performed as an urgent or emergent procedure, and the patient must be in good condition prior to surgery. The benefit of thymectomy is realized over a long period, generally years. As noted above, thymic abnormalities are less common in MuSK antibody-positive MG, and thymectomy is now rarely performed in these patients.

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Refractory Myasthenia Gravis

Although most MG patients respond to conventional treatment with the immunosuppressive agents described above, occasionally patients either fail to respond to appropriate doses of these agents, or cannot tolerate their adverse side effects. Treatment for these "refractory" patients has previously required resorting to repeated plasmapheresis or IVIG infusion, which provide only temporary benefit, are expensive and inconvenient, and may not produce satisfactory clinical results. Ideally, treatment for these patients should attempt to eliminate the autoimmune response, and provide long-term or permanent benefit. We have developed a method of using high-dose cyclophosphamide to "reboot" the immune system, with good results in the majority of otherwise refractory patients.[12] The use of high-dose cyclophosphamide transiently eliminates the mature immune system, while allowing the stem cells to repopulate it over several weeks. The method requires special attention, and should be used only under the supervision of experts in this area of hematology/oncology.

Drugs to Avoid in Myasthenia Gravis

There are many drugs that can exacerbate MG and should be avoided. The most common problems arise with antibiotics that are quinolone derivatives (e.g., ciprofloxacin, moxifloxacin, levofloxacin) or aminoglycosides (gentamicin, tobramycin, streptomycin). Other drugs that may exacerbate MG include quinine, local anesthetics, β blockers, muscle relaxants used in surgery (e.g., curariform agents), and botulinum toxin. A list of these agents is available on the Myasthenia Gravis Foundation of America website (http://www.myasthenia.org/LivingwithMG/DrugstoAvoid.aspx).

Immunizations, Surgery, and Dentistry

Patients on immunosuppressive agents should never be immunized with live agents (e.g., yellow fever, Zostavax [Merck & Co.], or live polio vaccine). To allow the immune system to respond effectively to immunizations, mycophenolate should be stopped at least 3 to 4 days before the immunization, and not restarted until approximately 4 days later. Even so, immunization may be incomplete. Major surgery may result in exacerbation of MG, and most patients should be pretreated with IVIG to help them get through the surgery. Before dental procedures, MG patients who are on immunosuppressive agents should be given 2 g of amoxicillin approximately 1 hour before the procedure.

When and How to Use Intravenous Anticholinesterase Agents

Patients who cannot swallow may require intravenous anti-ChE agents. I use 1 mg of neostigmine per 60 mg of oral pyridostigmine that the patient usually takes. The IV neostigmine should be infused, not given as IV boluses. An IV bolus has a short lifespan. Infusion pumps give more reliable and consistent results. Calculate the total amount per 24 hours, and infuse it over the entire 24-hour period. If a patient is on ventilator support, parenteral anti-ChE drugs are useful only if they are helpful in allowing the patient to be extubated. Otherwise, stop the parenteral anti-ChE drugs. A "drug holiday" of 48 to 96 hours may reduce desensitization, and when restarted the drug may be more effective.

The Most Common Errors in Managing Myasthenia Gravis

1. Delay in considering the diagnosis of MG.
2. Starting treatment before making a definitive diagnosis
3. Using excessively high doses of anti-ChE medications.
4. Using "standard" doses of immunosuppressive drugs, rather than adjusting to the individual patient's needs.
5. Waiting before treating intercurrent infection.
6. Waiting too long before treating imminent crisis.
7. Tapering immunosuppressive medications too rapidly or too far.
8. Carrying out thymectomy without adequate preparation or on an "emergency" basis.
9. Not following the patient's MG and general medical problems closely enough.
10. Trying to treat patients who are not compliant with medications without understanding the barriers to compliance.

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