MEDICAL PROGRESS

HYPERBARIC-OXYGEN THERAPY

Patrick M. Tibbles, M.D.,
and John S. Edelsberg, M.D., M.P.H.

Hyperbaric oxygen — 100 percent oxygen at two to three times the atmospheric pressure at sea level — can result in arterial oxygen tension in excess of 2000 mm Hg1 and oxygen tension in tissue of almost 400 mm Hg.2,3 Such doses of oxygen have a number of beneficial biochemical, cellular, and physiologic effects, and today there are 259 hyperbaric facilities in the United States with 344 single-occupant (“monoplace”) hyperbaric-oxygen chambers.4 In this article, we review the mechanisms of action, evidence of clinical efficacy, and risks of therapy with hyperbaric oxygen.

Physiologic Effects

For hyperbaric oxygen, pressure is expressed in multiples of the atmospheric pressure at sea level, which is 1 atmosphere (1 atmosphere = 14.7 psi, 1 kg per square centimeter, 101.3 kPa, 760 torr, or 760 mm Hg). At sea level the blood (plasma) oxygen concentration is 0.3 ml per deciliter.5,6 Tissues at rest extract 5 to 6 ml of oxygen per deciliter of blood, assuming normal perfusion.7,8 Administering 100 percent oxygen at ambient (normobaric) pressure increases the amount of oxygen dissolved in the blood fivefold to 1.5 ml per deciliter, and at 3 atmospheres, the dissolved-oxygen content is approximately 6 ml per deciliter, more than enough to meet resting cellular requirements without any contribution from oxygen bound to hemoglobin.

The sudden formation of inert-gas bubbles in blood vessels and tissues causes decompression sickness and air embolism. Boyle’s law, which states that the volume of gas in an enclosed space is inversely proportional to the pressure exerted on it, governs this process and explains some of the beneficial effects of hyperbaric oxygen in conditions caused by the formation of gas bubbles. At 2.8 atmospheres, bubble volume is reduced by almost two thirds. In addition, hyperbaric oxygen hastens the dissolution of the inert-gas bubble by replacing the inert gas in the bubble with oxygen, which is then rapidly metabolized by the tissues. The use of hyperbaric oxygen also prevents the formation of new bubbles.

Biochemical and Cellular Effects

Local hypoxia predisposes wounds to infection, because the neutrophil-mediated killing of bacteria by free radicals is decreased.9 Hyperbaric oxygen restores this defense against infection and increases the rate of killing of some common bacteria by phagocytes.10 In addition, hyperbaric oxygen alone is bactericidal for certain anaerobes, including Clostridium perfringens,9 and bacteriostatic for certain species of escherichia11,12 and pseudomonas.12 It also suppresses clostridial production of alpha toxin.13,14

Local hypoxia leads to poor wound healing. Adequate oxygen tension is a prerequisite for the formation of collagen matrix, which is essential for angiogenesis.15,16 In irradiated tissue, hyperbaric oxygen is more effective than normobaric oxygen in increasing the partial pressure of oxygen to a level that promotes the formation of collagen matrix and angiogenesis.17 Whether hyperbaric oxygen is superior to 40 to 100 percent normobaric oxygen in improving wound healing in nonirradiated tissue is not clear.18-20

Reperfusion injury can worsen crush injuries and compartment syndromes and cause skin flaps and reattachment procedures to fail. Neutrophils have been implicated as the prime endogenous culprit in reperfusion injury.21 Adhering to the walls of ischemic vessels, they release proteases and produce free radicals, leading to pathologic vasoconstriction and extensive tissue destruction.22 Hyperbaric oxygen inhibits neutrophil adherence and postischemic vasoconstriction in ischemic rat tissue.23,24

Since the pioneering work of Bernard in the 1850s, the toxic effects of carbon monoxide have been attributed primarily to its indirect inhibition of cellular respiration by its reversible binding to hemoglobin.24 Hyperbaric oxygen at 2.5 atmospheres reduces the half-life of carboxyhemoglobin from 4 to 5 hours in subjects breathing room air to 20 minutes or less.25 Two additional beneficial effects of hyperbaric oxygen in carbon monoxide poisoning have been established. In vitro, carbon monoxide binds to a component of the electron-transport chain (cytochrome-c oxidase), leading to cellular asphyxiation. The dissociation of carbon monoxide from this enzyme by hyperbaric oxygen is postulated to account for some of the efficacy of this therapy.26,27 In rats with carbon monoxide–mediated brain injury, neutrophils appeared to trigger an enzymatic process leading to the formation of oxygen radicals and neuronal death from lipid peroxidation.28,29 The timely administration of hyperbaric oxygen to these animals prevented neuronal injury in a dose-dependent fashion by an unknown mechanism.30,31

Administration

To be effective, hyperbaric oxygen must be inhaled in the atmosphere or through an endotracheal tube in a monoplace chamber (Fig. 1), or through masks, tight-fitting hoods, or endotracheal tubes in a larger, multi-occupant chamber. The duration of single treatments varies from 45 minutes for carbon monoxide poisoning to almost 5 hours for some severe decompression disorders. For treatment of wounds that do not respond to débride-
ment or antibiotics — that is, problem wounds — most protocols average 90 minutes for each of 20 to 30 treatments. Critical care monitoring and treatment, including mechanical ventilation, should be readily available. Their portability, minimal personnel requirements, and relatively low cost have made monoplace chambers the most common type of chamber worldwide.32

**Therapeutic Uses of Hyperbaric Oxygen**

**Carbon Monoxide Poisoning**

Carbon monoxide poisoning, primarily from smoke inhalation and suicide attempts, is the most common cause of death by poisoning in the United States.33,34 Although there is no universally accepted scheme for grading the severity of carbon monoxide poisoning, severe poisoning is indicated by loss of consciousness (syncope, seizures, and coma), neurologic deficits, pulmonary edema, myocardial ischemia, and severe metabolic acidosis. Less severely poisoned patients may have headache, nausea, and other constitutional symptoms. In addition to the acute toxic effects, all victims of carbon monoxide poisoning are at risk for delayed neuropsychological sequelae. Carboxyhemoglobin levels do not correlate well with the clinical severity of carbon monoxide poisoning.

Numerous nonrandomized studies have found that hyperbaric oxygen reverses both the acute and the delayed effects of carbon monoxide poisoning.35 However, two trials comparing hyperbaric oxygen with normobaric oxygen delivered outside a hyperbaric chamber in patients with no loss of consciousness had conflicting results36,37; in a third trial, in which 17 of 26 patients had transient loss of consciousness, hyperbaric oxygen was beneficial (Table 1).38 An early analysis of data on 50 patients with acute carbon monoxide poisoning who were enrolled in a trial of hyperbaric oxygen as compared with normobaric oxygen delivered in a hyperbaric chamber (a true sham control) revealed no difference in persistent or delayed neuropsychological sequelae between the treatment groups (Table 1).39

Because hyperbaric oxygen is the fastest method of reversing the potentially life-threatening effects of acute carbon monoxide poisoning, we think that patients with severe carbon monoxide poisoning should receive at least one treatment with hyperbaric oxygen at 2.5 to 3.0 atmospheres; additional treatments may produce greater improvement in neuropsychological deficits. For patients with lesser degrees of poisoning, we advise consultation with a toxicologist to determine whether the administration of 100 percent normobaric oxygen for four to six hours, or until symptoms abate, would be adequate therapy.

**Decompression Sickness**

When recreational divers breathing compressed air return to the water surface too rapidly, the partial pressure of nitrogen dissolved in their tissues and blood may exceed the ambient pressure. Gas bubbles then form in the tissues and blood, causing a disease called decompression sickness. Affected divers may have a spectrum of symptoms ranging from self-limited rash to paralysis, seizures, and even death as a result of the blocking of lymphatics, veins, and arteries by the gas bubbles. Each year in the United States, approximately 500 recreational divers using self-contained underwater breathing apparatus (scuba) have decompression sickness.47 Although it is largely a disease of divers, persons ascending above 5500 m can also have decompression sickness (altitude decompression sickness).48

Reduction in bubble size and correction of hypoxia have been considered the primary mechanisms by which hyperbaric oxygen benefits patients with decompression sickness. In this disorder, biochemical actions at the blood–gas interface lead to alterations in hemostasis, endothelial damage, and activation of leukocytes.49 The beneficial effect of hyperbaric oxygen on these pathologic mechanisms may play a more important part in clinical improvement than the reduction in the size of bubbles and the correction of hypoxia.

Thousands of favorable responses to early therapy with hyperbaric oxygen during the past 50 years have established it as the primary treatment for decompression sickness, although no randomized trials have compared hyperbaric with normobaric oxygen. Patients who have decompression sickness should receive hyperbaric oxygen at 2.5 to 3.0 atmospheres for two to four hours, with repeated or longer treatment as necessary until they are symptom-free or there is no further clinical improvement. The outcome is more likely to be successful if therapy is begun within six hours after the onset of symptoms.50

**Arterial Gas Embolism**

Arterial gas embolism can arise from pulmonary overinflation during a dive, often as a consequence of uncontrolled ascent to the surface, or during mechanical ventilation. This disorder can also result from the placement of a central venous catheter, cardiothoracic surgery, hemodialysis, and oral–vaginal sex during pregnancy.51-53 Immediate therapy with hyperbaric oxygen, typically at 2.5 to 3.0 atmospheres for two to four hours, is the treatment of choice, given the well-established pathophysiology of arterial gas embolism and numerous reports of improvement immediately after hyperbaric treatment.50 Such treatment improves outcome in these patients by the mechanisms described for decompression sickness.

**Radiation-Induced Tissue Injury**

Irradiated tissues lose the capacity for restorative cellular proliferation, leading to decreased vascularity, local hypoxia, and eventually, necrosis.54 This loss manifests itself clinically as edema, ulceration, bone necrosis, increased risk of infection, and poor wound healing, processes that can persist for years.55 One hundred percent oxygen at 1 atmosphere produces insufficient tissue oxygen gradients for wound healing in irradiated tissue, but higher arterial partial pressures of oxygen result in new blood-vessel growth and partial healing.56 Before hyperbaric-oxygen therapy was available, reconstruction of previously irradiated mandibular tissue in patients with oropharyngeal and other head and neck tumors was often unsuccessful, with complications, including osteonecrosis, soft-tissue radio-
necrosis, mucositis, dermatitis, and laryngeal radionecrosis, developing in 50 to 60 percent of patients. With hyperbaric oxygen, success rates of up to 93 percent have been reported among selected patients.41,57-59

In an unblinded, controlled trial, 30 hyperbaric-oxygen treatments were more effective in preventing the development of mandibular osteoradionecrosis than penicillin in 37 previously irradiated patients (Table 1).40 In a preliminary analysis of 160 irradiated patients undergoing soft-tissue flap surgery, preoperative therapy with hyperbaric oxygen was superior to routine care in reducing wound dehiscence, infections, and delayed wound healing.41 Current protocols for the prevention and treatment of osteoradionecrosis involve 30 preoperative hyperbaric-oxygen sessions at 2.4 atmospheres for 90 minutes each, followed by 10 treatments after surgery.

Clostridial Myonecrosis

Although clostridia commonly contaminate traumatic wounds, clostridial myonecrosis, a rapidly progressive, life-threatening infection, is rare. In this disease, clostridial production of toxins, especially alpha toxin, leads to extensive tissue destruction and shock. Although classically associated with traumatic wounds in war, clostridial myonecrosis occurs almost as often after abdominal surgery as it does after traumatic wounds, and cases have been reported after bee stings and venipuncture. The patients present with pain out of proportion to the apparent severity of their wounds and often have evidence of tissue gas (gas gangrene).

The mainstay of treatment of clostridial myonecrosis has always been immediate surgical decompression and excision of all necrotic tissue. Penicillin remains the most effective antimicrobial drug. In a study comparing treatment of clostridial myonecrosis in dogs with and without hyperbaric oxygen (in combination with surgery and antibiotics), the respective survival rates were 95 percent and 70 percent (P = 0.05).60 More than 1200 cases of clostridial myonecrosis treated with hyperbaric oxygen have been reported.61 The available clinical and experimental evidence suggests that multiple early treatment sessions with hyperbaric oxygen at 3 atmospheres for 90 minutes, when administered in conjunction with antibiotics and surgery, confer the following benefits: the border between devitalized and healthy tissue is more clearly demarcated, permitting surgeons to be more conservative in their excisions; the extent of amputation required in clostridial myonecrosis involving the extremities is decreased; and systemically ill patients often improve substantially after one or two treatments.

Necrotizing Fasciitis

Rapidly progressive infections of the skin and underlying tissue without muscle involvement are most commonly referred to as necrotizing fasciitis. Mortality is high. Because these infections have similarities to clostridial myonecrosis, hyperbaric oxygen in conjunction with surgery and antibiotic therapy has been used to treat them, although fewer patients have been treated with hyperbaric oxygen for necrotizing fasciitis than for clostridial myonecrosis. Hyperbaric oxygen was effective in two of four small observational studies in humans, some with historical controls.62-65

Refractory Osteomyelitis

Hyperbaric oxygen has proved effective in the treatment of experimental osteomyelitis in rabbits66 and has greatly improved the outcome in patients with chronic osteomyelitis that is unresponsive to standard surgical and antibiotic therapy.67 In a study comparing hyperbaric-oxygen therapy with no additional therapy beyond surgical débridement and antibiotics in 28 patients with chronic refractory osteomyelitis, there was no difference between the groups in length of hospitalization (mean, 54 days) or clinical outcome.68 However, because more than 90 percent of the patients in the group that did not receive hyperbaric oxygen were cured, the definition of “refractory osteomyelitis” in this study is suspect. Hyperbaric oxygen at 2.0 to 2.5 atmospheres for 90 to 120 minutes after débridement in combination with antibiotic therapy can improve healing.

Acute Traumatic Ischemic Injury

Crush injury and other severe trauma to the extremities can result in tears of the major vessels and damage to the microcirculation, with resultant ischemia, edema, compartment syndromes, and tissue necrosis. Surgery remains the cornerstone of therapy for these injuries. Reduction of edema, protection from reperfusion injury, and enhanced wound healing are postulated benefits of adjunctive therapy with hyperbaric oxygen.
Hyperbaric oxygen was more effective than no treatment in animals with experimentally induced ischemia and compartment syndromes. Although many case reports and case series suggest a benefit of hyperbaric oxygen, it has not been compared with normobaric oxygen in patients or animals with acute traumatic ischemic injury. Perioperative protocols involve treatment at pressures ranging from 2.0 to 2.8 atmospheres for up to two hours.

Compromised Skin Grafts and Flaps

Skin grafts and reconstructive flaps may fail because of inadequate perfusion and hypoxia. Graft or flap failure is less frequent in animals receiving hyperbaric oxygen than in those receiving no treatment. In a series of 105 patients, hyperbaric oxygen reversed distal-flap ischemia and increased the rate of successful grafting in poorly vascularized tissue. In a group of 46 patients receiving split-thickness skin grafts, the graft survival rates were higher in the patients treated with hyperbaric oxygen (Table 1). Hyperbaric-oxygen treatments at 2.0 to 2.5 atmospheres for 90 to 120 minutes each should be considered when a graft or flap must be placed over a capillary bed with poor circulation, especially if previous reconstruction in the same area was unsuccessful.

Anemia Due to Exceptional Blood Loss

Under hyperbaric conditions, the amount of oxygen dissolved in the blood can be sufficient to meet cellular metabolic demands without any contribution from oxygen transported by hemoglobin. Hyperbaric oxygen has been used successfully to treat hemorrhagic shock in patients for whom suitable blood was not available or who refused transfusion for religious reasons.

Thermal Burns

The postulated mechanisms of a beneficial effect of hyperbaric oxygen on burn wounds are decreased edema due to hyperoxic vasoconstriction, increased

Table 1. Summary of Randomized, Controlled Trials of Hyperbaric Oxygen for Current Therapeutic Uses.*

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Indications</th>
<th>Control Therapy</th>
<th>Type of Hyperbaric Oxygen</th>
<th>P Value</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raphael et al.</td>
<td>343</td>
<td>Carbon monoxide poisoning without loss of consciousness</td>
<td>100% normobaric oxygen</td>
<td>Not blinded</td>
<td>Symptom of carbon monoxide poisoning or neurologic deficits assessed by physical examination and questionnaire</td>
<td>0%</td>
</tr>
<tr>
<td>Thom et al.</td>
<td>65</td>
<td>Carbon monoxide poisoning without loss of consciousness</td>
<td>100% normobaric oxygen</td>
<td>Not blinded</td>
<td>Acute neurosensory symptoms</td>
<td>0%</td>
</tr>
<tr>
<td>Ducasse et al.</td>
<td>26</td>
<td>Carbon monoxide poisoning in patients with transient loss of consciousness, mild neurologic deficits, or constitutinal symptoms</td>
<td>100% normobaric oxygen</td>
<td>“Open and blinded”</td>
<td>Symptoms and abnormal physical examination at 12 hr</td>
<td>0%</td>
</tr>
<tr>
<td>Weaver et al.</td>
<td>50</td>
<td>Carbon monoxide poisoning with and without loss of consciousness</td>
<td>100% oxygen at 1.0 atmosphere in hyperbaric chamber</td>
<td>Blinded</td>
<td>Persistent and delayed neurosensory sequelae</td>
<td>16%†</td>
</tr>
<tr>
<td>Marx et al.</td>
<td>74</td>
<td>Dental extraction after mandibular irradiation</td>
<td>Penicillin for 10 days</td>
<td>Not blinded</td>
<td>Osteoradionecrosis at 6 mo</td>
<td>5%</td>
</tr>
<tr>
<td>Marx</td>
<td>160</td>
<td>Major soft tissue surgery, including flap placement, after irradiation</td>
<td>Reparative surgery</td>
<td>Unknown</td>
<td>Wound dehiscence</td>
<td>11%</td>
</tr>
<tr>
<td>Perrins</td>
<td>48</td>
<td>Every patient presenting for split-skin grafting</td>
<td>Surgery and routine wound care</td>
<td>Not blinded</td>
<td>Mean percentage of permanent graft survival</td>
<td>84%</td>
</tr>
<tr>
<td>Hart et al.</td>
<td>16</td>
<td>Thermal burns over 10–50% of the body</td>
<td>Usual burn care at the time and 21% oxygen at 1.3 atm. in hyperbaric chamber</td>
<td>Blinded</td>
<td>Mean healing time</td>
<td>20 days</td>
</tr>
<tr>
<td>Brannen et al.</td>
<td>125</td>
<td>Acute thermal burns</td>
<td>Usual burn care</td>
<td>Unknown</td>
<td>Length of hospital stay</td>
<td>21 days</td>
</tr>
<tr>
<td>Hammarsland and Sandberg</td>
<td>16</td>
<td>Leg ulcers in nondiabetic patients with no large-vessel disease</td>
<td>Air at 2.5 atmospheres</td>
<td>Blinded</td>
<td>Reduction in wound area at:</td>
<td>2%</td>
</tr>
<tr>
<td>Doctor et al.</td>
<td>30</td>
<td>Chronic diabetic foot lesions</td>
<td>Surgery, antibiotics, local wound care</td>
<td>Not blinded</td>
<td>Bacterial growth</td>
<td>3 patients</td>
</tr>
</tbody>
</table>

*NS denotes not as statistically significant (P value not given), and EEG electroencephalogram.
†Blinded interim analysis with treatment groups undefined at this time.
collagen formation, and improved phagocytic killing of bacteria. In a trial comparing burn treatment with and without hyperbaric oxygen in 16 patients, the mean healing time was significantly shorter in the group receiving hyperbaric oxygen (Table 1). Among 266 patients with burns who were treated with hyperbaric oxygen and 609 who were not, there were no significant differences in mortality and length of hospital stay. The preliminary results of a randomized, controlled trial of hyperbaric oxygen at a burn center in Augusta, Georgia, were reported recently; among 125 patients randomly assigned to usual burn care or usual burn care plus hyperbaric oxygen, the outcomes were virtually identical (Table 1).

During the past two decades, there have been many advances in burn therapy, including improved respiratory care, better use of topical and parenteral antibiotics, early débridement, and parenteral nutrition. At this time it is not clear that hyperbaric oxygen confers any benefits when added to the usual care provided to patients in burn centers.

**Problem Wounds**

In this country, hyperbaric oxygen is used for problem wounds, especially diabetic foot infections and leg ulcers caused by arterial insufficiency, more than for any other indication.

In a study comparing 62 diabetic patients with foot ulcers who were treated with hyperbaric oxygen (an average of 72 treatments per patient), 18 similar patients unable or unwilling to undergo therapy with hyperbaric oxygen, and 49 patients treated before the availability of hyperbaric oxygen at the same institution, Oriani et al. found amputation rates of 4, 49, and 39 percent, respectively. In a prospective, double-blind study of 16 nonsmokers with chronic leg ulcers but with no large-vessel disease or major chronic illnesses who received 30 treatments with either hyperbaric oxygen or hyperbaric air, the wound area had decreased more at four and six weeks in the patients treated with hyperbaric oxygen (Table 1). It is not clear that these results can be generalized to the majority of patients with problem wounds, many of whom are smokers and have chronic illnesses such as vascular disease and diabetes. In a study of 30 diabetic patients with foot lesions treated with routine care or with routine care plus four 45-minute hyperbaric-oxygen treatments, fewer patients in the group receiving hyperbaric oxygen required above-the-ankle amputation (Table 1). It is not clear why improvement occurred with so few treatments, when in other studies a minimum of 30 treatments was necessary to improve healing.

Measurements of the transcutaneous oxygen tension are useful for evaluating the severity of peripheral vascular disease and the healing potential of lower-extremity wounds. A trial of adjunctive therapy with hyperbaric oxygen at 2.0 to 2.5 atmospheres for 90 to 120 minutes may be reasonable in patients with problem wounds if arterial insufficiency has been appropriately treated, maximal antibiotic therapy has been given, and the transcutaneous oxygen tension around the wound increases during exposure to hyperbaric oxygen.

**Adverse Effects**

When used according to standard protocols, with oxygen pressures not exceeding 3 atmospheres and treatment sessions limited to a maximum of 120 minutes, hyperbaric therapy is safe. However, some adverse effects may occur. Reversible myopia, a consequence of the direct toxic effect of oxygen on the lens, is the most common side effect. Cataract formation, however, has not been seen in patients treated according to standard protocols. A few patients may experience mild-to-severe pain from rupture of the middle ear, the cranial sinuses, and, in rare cases, the teeth or lungs as a result of rapid pressure changes — that is, barotrauma. Inhalation of high concentrations of oxygen under pressure may precipitate generalized seizures, but these are rare and self-limited, and cause no permanent damage.

With repeated exposure to hyperbaric oxygen, some patients have reversible tracheobronchial symptoms — chest tightness, a substernal burning sensation, and cough— with concomitant reversible decrements in pulmonary function. Critically ill patients who have required high concentrations of normobaric oxygen for a prolonged period and then undergo repeated exposure to hyperbaric oxygen are at greater risk for toxic pulmonary effects. Claustrophobia can be a problem in monoplace chambers. No evidence of a tumorigenic effect of hyperbaric oxygen has been found to date.

**Cost**

An average 90-minute hyperbaric-oxygen treatment in the United States costs between $300 and $400. The cost of 30 to 40 sessions for the treatment of radione-
cross or problem wounds can therefore range from $9,000 to $16,000. A simple economic analysis of hyperbaric-oxygen therapy and surgery in patients with osteoradionecrosis, however, reported a savings of $96,000 as compared with in-hospital, nonhyperbaric-oxygen therapy.11

CONCLUSIONS

Hyperbaric oxygen has been described as “a therapy in search of diseases.”88 Many of its past uses had little or no scientific support. The discovery of beneficial cellular and biochemical effects has strengthened the rationale for administering hyperbaric oxygen as primary therapy in patients with severe carbon monoxide poisoning, decompression sickness, and arterial gas embolism, and as adjunctive therapy for the prevention and treatment of osteoradionecrosis, clostridial myonecrosis, and compromised skin grafts and flaps. The physiologic effects of hyperbaric oxygen on plasma oxygen content make this therapy the treatment of choice in severe anemia when transfusion is not an option. There is less scientific support for the other uses of hyperbaric oxygen, although reports of favorable effects support many of them.

In Table 2 we have attempted to aid clinicians in their decision making by categorizing the indications for hyperbaric-oxygen therapy proposed by the Undersea and Hyperbaric Medical Society.89 The paucity of randomized, controlled trials makes it difficult to assess the efficacy of hyperbaric oxygen in most diseases. In diseases for which the use of hyperbaric oxygen is not well supported, the potential benefits must be carefully weighed against the risks of transferring the patient, if necessary, and the cost.

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